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Elina Urpilainen

THE ROLE OF METFORMIN AND STATINS IN OVARIAN AND BREAST CANCER IN WOMEN WITH TYPE 2 DIABETES

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THE ROLE OF METFORMIN AND STATINS IN OVARIAN AND BREAST CANCER IN WOMEN WITH TYPE 2 DIABETES

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Abstract

Patients with type 2 diabetes (T2D) are at a greater risk of some cancer types, possible together with worse prognosis. Various types of antidiabetic medication have been reported to have different relationships to cancer prognosis. Metformin seems to reduce mortality in some forms of cancer and it has effects on cell cycle arrest and apoptosis *in vitro*. T2D is a risk factor of coronary heart disease, which is widely treated with statins. Statins are associated with both reduced incidence and better prognosis in some cancers. Epidemiological studies on the associations between metformin and statin use and breast and ovarian cancer have reported inconclusive results.

The aim of the present epidemiological study was to find out whether metformin and statin use are associated with reduced incidence and mortality in ovarian and/or breast cancer. The source population for the study was drawn from the Finnish nationwide diabetes database (FinDM; n = 244,322), supplemented with other Finnish registry data. The data from FinDM was combined with data from the Finnish Cancer Registry.

The use of metformin and/or statins was found not to be associated with the incidence of either ovarian (n=303) or breast cancer (n=2,300) in women with type 2 diabetes. The use of insulin seemed to be associated with a higher incidence of breast cancer. Metformin use was not observed to be associated with mortality from ovarian or breast cancer but mortality from other causes seemed to be lower in breast cancer patients among metformin users compared with the users of other types of oral antidiabetic medication. Prediagnostic statin use seemed to be associated with decreased mortality from breast cancer and other causes in breast cancer patients, but in ovarian cancer, an association with reduced mortality was seen only in connection with ovarian cancer itself.

On the basis of our study results, it would not be reasonable to initiate metformin or statin treatment solely in order to avoid ovarian or breast cancer development in a woman with T2D. However, the results suggest that tailoring of glycaemic and hypercholesterolaemia treatment might have far-reaching consequences to both cancer development and survival.

Keywords: breast cancer, epidemiology, metformin, ovarian cancer, statins, type 2 diabetes

Urpilainen, Elina, Metformiini ja statiinit munasarja- ja rintasyövässä tyypin 2 diabetesta sairastavilla naisilla.
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Tiivistelmä

Tyypin 2 diabetesta sairastavilla potilailla on yleensä suurentunut riski sairastua maksa-, haima- ja suolistosyöpiin, ja tämä heikentää ainakin näiden syöpien ennustetta. Diabeteslääkkeillä on todettu olevan toisistaan poikkeava vaikutus syöpäennusteeseen. Metformiini vaikuttaa alentavan kuolleisuutta, ja solutöissä sillä on todettu olevan vaikutuksia solusyklin pysähtymiseen ja ohjelmoituun solukuolemaan. Tyypin 2 diabetes on riskitekijä sydän- ja verisuonisairauksiin, ja sen vuoksi diabetespotilaiden hoitoon kuuluu usein kolesterolia alentavat statiinit. Statiinien käyttö on yhdistetty joidenkin syöpäsairauksien vähenemiseen ja niiden parempaan ennusteeseen. Epidemiologiset tutkimukset metformiinin ja statiinien käytön välisestä yhteydestä munasarja- ja rintasyöpiin ovat kuitenkin epäyhtenäisiä.

Tutkimuksen tarkoituksena oli selvittää, onko metformiinin ja statiinien käytöllä yhteyttä munasarja- ja rintasyöpätapausten vähenemiseen ja niiden paranemisennusteeseen. Lähdeaineistona on käytetty erilaisia suomalaisia rekistereitä yhdistävää kansallista diabetes-tietokantaa (FinDM; n = 244 322), jonka tiedot on yhdistetty Suomen Syöpärekisteriin.

Metformiinin ja statiinien käytöllä ei todettu olevan yhteyttä munasarjasyövän (n = 303) tai rintasyövän (n = 2 300) ilmaantuvuuteen tyypin 2 diabetesta sairastavilla naisilla. Insuliinin käytöllä oli sen sijaan yhteys korkeampaan rintasyövän ilmaantuvuuteen. Metformiinin käytöllä ei todettu olevan yhteyttä munasarja- tai rintasyöpäkuolleisuuteen. Rintasyöpää sairastavilla naisilla muista syistä johtuva kuolleisuus oli metformiinin käyttäjillä kuitenkin matalampaa verrattaessa muihin suun kautta otettavien diabeteslääkkeiden käyttäjiin. Ennen syöpädiagnoosia aloitettu statiinien käyttö vaikutti vähentävän kuolleisuutta sekä rintasyöpään että muihin syihin rintasyöpäpotilailla. Munasarjasyövän suhteen yhteys todettiin ainoastaan munasarjasyöpäkuolleisuudessa.

Tutkimuksemme mukaan ei ole perusteltua aloittaa metformiinia tai statiineja tyypin 2 diabetesta sairastavalle naiselle pelkästään ehkäisemään munasarja- tai rintasyöpää. Kuitenkin tutkimuksemme osoittaa, että niin diabetes- kuin kolesterolilääkityksellä voi olla yhteyttä sekä syövän kehittymiseen että paranemisennusteeseen.

Asiasanat: epidemiologia, metformiini, munasarjasyöpä, rintasyöpä, statiinit, tyypin 2 diabetes

To Elmo

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Oulu, October 2019 *Elina Urpilainen*

Abbreviations

ACC	acetyl-coenzyme A carboxylase
ADM	antidiabetic medication
aHR	adjusted hazard ratio
AKT	serine/theonine-specific protein kinase
AMPK	AMP-activated protein kinase
AMP	adenosine monophosphate
BMI	body mass index
BRCA1	breast cancer susceptibility gene 1
BRCA2	breast cancer susceptibility gene 2
BRIP1	BRCA1-interacting protein 1
CDH1	chromodomain helicase DNA binding protein 1
cDNA	complementary deoxyribonucleic acid
CHEK2	checkpoint kinase 2
CI	confidence interval
DDD	defined daily dose
DFS	disease free survival
DM	diabetes mellitus
DPP-4	dipeptidyl peptidase-4
DSM	disease specific mortality
ER	oestrogen receptor
ERK	extracellular signal-regulated kinase
FCR	Finnish Cancer Registry
FinDM	‘Diabetes in Finland’ database
GDM	gestational diabetes mellitus
GLP-1	glucagon-like peptide-1 agonist
HbA1c	glycated haemoglobin
HER2	human epidermal growth factor receptor 2
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HR	hazard ratio
HRT	hormone replacement therapy
i.e.	id est
IGF-1	insulin-like growth factor 1
IQR	interquartile range
MLH1	MutL homolog 1
MSH2	DNA mismatch repair protein, MutS protein homolog 2

MSH6	MutS homolog protein 6
mTOR	mammalian target of rapamycin
OGTT	oral glucose tolerance test
OR	odds ratio
OS	overall survival
p53	tumour protein p53
PALB2	partner and localizer of breast cancer susceptibility gene 2 (BRCA2)
PARP	poly ADP ribose polymerase
PCOS	polycystic ovary syndrome
PFS	progression-free survival
PIC	personal identity code
PR	progesterone receptor
PTEN	phosphatase and tensin homolog
RFS	recurrence-free survival
RR	risk ratio
SGLT2	sodium-glucose co-transporter 2
SIR	standardised incidence ratio
STIC	serous tubal intraepithelial carcinoma
STK11	serine/threonine kinase 11
T1D	type 1 diabetes
T2D	type 2 diabetes
TNM	Tumour-Node-Metastasis
WHI	Women’s Health Initiative

List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

I Urpilainen, E., Marttila, M., Hautakoski, A., Arffman, M., Sund, R., Ilanne-Parikka, P., Arima, R., Kangaskokko, J., Puistola, U., Läärä, E., & Hinkula, M. (2018) The role of metformin and statins in the incidence of epithelial ovarian cancer in type 2 diabetes: a cohort and nested case-control study. *BJOG,* 125(8):1001-1008. doi: 10.1111/1471-0528.15151.

II Urpilainen, E., Marttila, M., Hautakoski, A., Arffman, M., Sund, R., Ilanne-Parikka, P., Arima, R., Kangaskokko, J., Puistola, U., Hinkula, M., & Läärä, E. (2018) Prognosis of ovarian cancer in women with type 2 diabetes using metformin and other forms of antidiabetic medication or statins: a retrospective cohort study. *BMC Cancer,* 18(1):767. doi: 10.1186/s12885-018-4676-z.

III Hosio, M.,* Urpilainen, E.,* Marttila, M., Hautakoski, A., Arffman, M., Sund, R., Puistola, U., Läärä, E., Jukkola, A., & Karihtala, P. (2019) Association of antidiabetic medication and statins with breast cancer incidence in women with type 2 diabetes. *Breast Cancer Research and Treatment,*175(3):741-748. doi: 10.1007/s10549-019-05185-0.

IV Hosio, M.,* Urpilainen, E.,* Hautakoski, A., Marttila, M., Arffman, M., Sund, R., Ahtikoski, A., Puistola, U., Karihtala, P., Jukkola, A., & Läärä, E. Survival in cases of breast cancer in women with type 2 diabetes using antidiabetic medication and statins: a retrospective cohort study. Manuscript.

* Equal contribution.

Contents

1 Introduction

Great interest in the possible cancer-preventive role of metformin arose in 2005 when an observational study from Scotland was published in which metformin use was related to a lower risk of cancer in general (Evans, Donnelly, Emslie-Smith, Alessi, & Morris, 2005). Since then, several epidemiological studies have been conducted on this subject. However, the possible association may vary according to the type of cancer. Therefore, it is more reasonable to study cancer types separately. As regards women's health, breast cancer is the most common and ovarian cancer is one of the most lethal gynaecological cancers globally (Ferlay et al., 2019).

Type 2 diabetes (T2D) is linked to an increased risk and worse prognosis of cancers (Currie et al., 2012; Giovannucci et al., 2010). However, the association between T2D and cancer is at least partly due shared risk factors (Boyle et al., 2012). In addition, antidiabetic medication (ADM) is known to modulate many T2D risk factors (Onitilo et al., 2012). Also, the association between different ADMs and cancer is complicated by polypharmacy, and segregation of a single medication and its association with cancer incidence or prognosis can be challenging (Onitilo et al., 2012).

In a recent meta-analysis (G. H. Tang et al., 2018) no association between metformin use and a reduced incidence of breast cancer was reported. On the other hand, it seemed that metformin use was related to a better prognosis of breast cancer (G. H. Tang et al., 2018). The association between metformin and ovarian cancer incidence is not clear ─ one group reported a lower incidence in metformin users (Tseng, 2015) and others have not been able to find such an association (Bodmer, Becker, Meier, Jick, & Meier, 2011; P. D. Home et al., 2010). In studies of survival after ovarian cancer, evidence of an association is also inconclusive (Bar, Lavie, Stein, Feferkorn, & Shai, 2016; Currie et al., 2012; Garcia, Yao, Camacho, Balkrishnan, & Cantrell, 2017; Romero et al., 2012).

Preclinical studies have suggested that metformin might have it all: anti-mitotic, anti-angiogenic and anti-inflammatory properties (Gadducci, Biglia, Tana, Cosio, & Gallo, 2016). Metformin has been widely studied in ovarian cancer cells and it seems that it inhibits growth of ovarian cancer cells (Rattan, Graham, Maguire, Giri, & Shridhar, 2011) and enhances the cytotoxic effect of chemotherapy (Shank et al., 2012). Also, metformin seems to have an oxidative stress-mediated effect on cell cycle arrest and apoptosis in breast cancer cells (Queiroz et al., 2014).

When studying the possible association between metformin use and cancer incidence and survival, the obvious study population consists of persons with T2D. Besides ADM, persons with T2D use statins widely (Vehko et al., 2013) because of an increased risk of cardiovascular diseases and hypercholesterolaemia (Reaven, 1988). Statin use is also reported to be linked to reduced cancer mortality (Nielsen, Nordestgaard, & Bojesen, 2012) and a decreased risk of cancer in general (Hu, Hu, & Fu, 2018). However, hypercholesterolaemia itself is associated with a poorer prognosis of breast cancer (Rodrigues, Fonseca, Dias, & Mendes, 2014) and an increased risk of ovarian cancer (A. J. Li, Elmore, Chen, & Karlan, 2010).

Regardless of all the attention around metformin and statins, the evidence is still inconclusive. Therefore, the aim in this study was to enrich the evidence between metformin and statin use and the incidence and prognosis of both ovarian and breast cancer by using highly reliable Finnish registry data.

2 Review of the literature

2.1 Type 2 diabetes mellitus

Type 2 diabetes mellitus is one of the most rapidly increasing chronic diseases globally. It is estimated that worldwide 425 million adults have diabetes, with more than 90% suffering from T2D, and their number is still increasing due to obesity, energy-dense diets and physical inactivity (IDF Diabetes Atlas, 2019; Chatterjee, Khunti, & Davies, 2017; Engelgau et al., 2004).

The diagnosis of T2D is based on increased fasting plasma glucose values (≥ 7 mmol), increased two-hour glucose values (> 11.0 mmol) in oral glucose tolerance tests (OGTTs) and/or increased glycated haemoglobin (HbA1c) values (≥ 48 mmol/mol, ≥ 6.5%) (Alberti & Zimmet, 1998; Type 2 diabetes: Current Care Guidelines, 2018).

Differentiation of T2D from type 1 diabetes (T1D) can sometimes be challenging, especially in younger patients. Diagnosis of T1D is usually based on absence of insulin-resistance markers and the results of biochemical tests, including low C-peptide concentrations and the presence of autoantibodies (Chatterjee et al., 2017).

2.1.1 Pathogenesis of T2D

Increased hyperinsulinaemia, insulin resistance and pancreatic β-cell failure are seen in T2D. Insulin resistance is determined as an inadequate insulin response in target tissues to the physiological effects of circulating insulin (Rochette, Zeller, Cottin, & Vergely, 2014).

The development of T2D concerns the pancreas, liver, skeletal muscle, kidneys, brain, small intestine and adipose tissue. Loss of pancreatic β-cell mass and function causes impaired insulin secretion and dysregulated glucagon secretion from pancreatic α-cells leading to increased glucagon concentrations. Hepatic glucose output is increased in T2D. Reduced peripheral glucose absorption both in the muscles and adipose tissue causes insulin resistance. Upregulation of sodium-glucose co-transporter 2 (SGLT2) receptors causes increased glucose uptake in the kidneys. Also, the glucose absorption rate is increased in the intestine and the microbiota in the colon is abnormal. In addition, patients with T2D have increased appetite (Chatterjee et al., 2017).

Unlike T2D, the pathogenesis of T1D results from a complex interaction between pancreatic β-cells and the immune system. The presentation of β-cell peptides by antigen-presenting cells is thought to cause the development of T1D. These antigen-presenting cells and autoantigens migrate to the pancreatic lymph nodes where they interact and activate T lymphocytes, which lyse β cells. β-cell destruction is increased by the release of proinflammatory cytokines and reactive oxygen species from immune cells. Activated T cells within the pancreatic lymph nodes also stimulate B lymphocytes to produce autoantibodies against β-cell proteins (DiMeglio, Evans-Molina, & Oram, 2018).

2.1.2 Risk factors of T2D

Obesity is the most important risk factor of T2D (Menke, Rust, Fradkin, Cheng, & Cowie, 2014). However, the distribution of fat matters, as abdominal obesity is the most harmful (J. M. Chan, Rimm, Colditz, Stampfer, & Willett, 1994). Also, an overweight condition, especially in childhood, seems to increase the risk (Bjerregaard et al., 2018). Family history is a strong independent risk factor of T2D (InterAct Consortium, 2013). Ethnicity is associated with T2D risk, as Asians, Hispanics and African Americans have an increased risk (Shai et al., 2006). Lifestyle factors also appear to be linked to the risk of T2D; physical inactivity (Crump, Sundquist, Winkleby, Sieh, & Sundquist, 2016), smoking (Willi, Bodenmann, Ghali, Faris, & Cornuz, 2007), short sleep duration (Gangwisch et al., 2007) and the so-called western diet (van Dam, Rimm, Willett, Stampfer, & Hu, 2002) all seem to increase the risk of T2D.

In addition to above, there are some medical conditions which are associated with a greater T2D risk. Women with prior gestational diabetes (GDM) have an increased risk of T2D (England et al., 2009). Cardiovascular diseases such as coronary artery disease and advanced heart failure are associated with a greater risk of T2D (Tenenbaum et al., 2003). Serum uric acid has been found to be an independent risk factor of T2D (Dehghan, van Hoek, Sijbrands, Hofman, & Witteman, 2008). Polycystic ovary syndrome (PCOS) was previously reported to be associated with an increased T2D risk (Joham, Ranasinha, Zoungas, Moran, & Teede, 2014), but in a recent Finnish study, the increased risk was not seen in normal-weight women with PCOS (Ollila et al., 2017). In women, it has also been observed that high serum testosterone levels are associated with an increased T2D risk (Ding, Song, Malik, & Liu, 2006). On the other hand, longer duration of

breastfeeding seems to be associated with a lower risk of T2D (Stuebe, Rich-Edwards, Willett, Manson, & Michels, 2005).

2.1.3 Cancer risk in T2D

Persons with T2D are at a greater risk of different types of cancer compared with persons without the condition (Giovannucci et al., 2010). However, it is not clear if T2D *per se* is causally linked to increased cancer risk in all cases. In some cancer types, T2D and cancer share the same risk factors, including obesity and an inactive lifestyle. Both hyperglycaemia and hyperinsulinaemia enhance cancer-cell proliferation and therefore T2D affects carcinogenesis and cancer-cell proliferation (Rose, Gracheck, & Vona-Davis, 2015; Wojciechowska, Krajewski, Bolanowski, Krecicki, & Zatonski, 2016). Thus, hyperglycaemia is associated with an increased cancer risk independently of obesity (Stattin et al., 2007). The menopause is known to be associated with increased adiposity and insulin resistance regardless of diet and therefore it is comprehensible that breast cancer risk is higher in postmenopausal women (Rose et al., 2015). The relationships between T2D, insulin resistance and cancer risk are shown in Figure 1.

A notably increased incidence of cancers is seen shortly after diagnosis of T2D which indicates a detection bias, as at recent diagnosis of T2D leads to increased medical attention (Carstensen, Witte, & Friis, 2012; Johnson, Bowker, Richardson, & Marra, 2011). A longer duration of T2D has not been associated with an increased cancer risk in general (Carstensen et al., 2012; Johnson et al., 2011). However, an Italian study reported an increased cancer risk with duration of T2D up to 10 years; after that, the risk being moderate to high (Ballotari et al., 2017).

It seems that T2D increases the incidence of (at least) cancers of the liver, pancreas, kidney (Giovannucci et al., 2010; Hemminki, Li, Sundquist, & Sundquist, 2010; Inoue et al., 2006), colorectum and endometrium (Giovannucci et al., 2010; Hemminki et al., 2010; Tsilidis, Kasimis, Lopez, Ntzani, & Ioannidis, 2015), in comparison with persons without T2D. In contrast, the incidence of prostate cancer has been reported to be lower in patients with T2D (Hemminki et al., 2010; Stattin et al., 2007).

Most studies have not found an association between T2D and ovarian cancer (Gapstur et al., 2012; Lambe et al., 2011; Parazzini et al., 1997; Weiderpass, Ye, Vainio, Kaaks, & Adami, 2002), but in one study, an increased risk of ovarian cancer was observed in hospitalised patients with T2D (Hemminki et al., 2010) (Table 1). The different result in the study by Hemminki et al. (2010) might be

explained by selection bias, as the hospitalised patients with T2D tended to have more complications and more severe T2D than the reference group, which included both patients with and without T2D.

In contrast to the above, most studies have reported an increased risk of breast cancer in women with T2D (Baron et al., 2001; Jee et al., 2005; Michels et al., 2003; Talamini et al., 1997), and only studies with mainly smaller sample sizes did not find any association (Franceschi, la Vecchia, Negri, Parazzini, & Boyle, 1990; Mink, Shahar, Rosamond, Alberg, & Folsom, 2002; Sellers et al., 1994; Weiss et al., 1999; Wideroff et al., 1997) (Table 2).

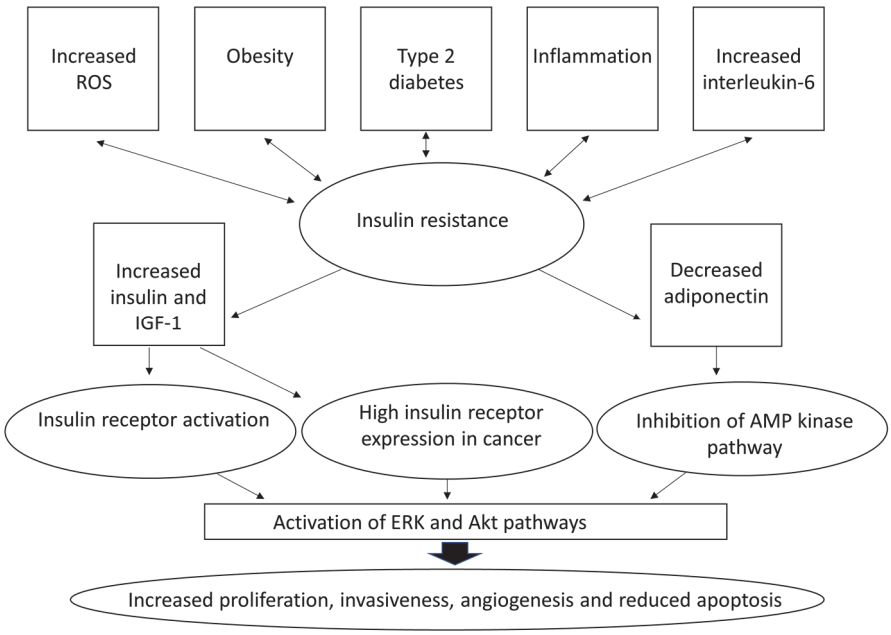

Fig. 1. Mechanisms that bind T2D, insulin resistance and cancer development together. IGF-1 = insulin-like growth factor-1, AMP = adenosine monophosphate, ERK = extracellular signal–regulated kinase, Akt = serine/threonine-specific protein kinase B, ROS = Reactive Oxygen Species. Modified after Ahmadieh & Azar (2013).

Table 1. Studies of ovarian cancer risk in women with diabetes compared with women without diabetes.

Study	Design	Country	Period	Patients	Main results
Parazzini et al. 1997	Case-control	Italy	1983–1991	971 ovarian cancers	RR 0.80 (95% CI 0.54–1.19)
Weiderpass et al. 2002	Register-based cohort	Sweden	1965–1994	Cohort size 141,627, 337 ovarian cancers	SIR 0.97 (95% CI 0.87–1.08)
Hemminki et al. 2010	Prospective cohort	Sweden	1964–2007	Cohort size 125,126, 192 ovarian cancers	SIR 1.84 (95% CI 1.59–2.12)
Lambe et al. 2011	Population-based cohort	Sweden	1985–1996	Cohort size 230,737, 783 ovarian cancers	HR 0.99 (95% CI 0.64–1.53)
Gapstur et al. 2012	Prospective cohort	USA	1992–2007	Cohort size 63,440, 524 ovarian cancers	RR 1.05 (95% CI 0.75–1.46)

CI = confidence interval, SIR = standardised incidence ratio, HR = hazard ratio, RR = relative risk

* Reported RRs are more likely to be HRs based on the study designs (Knol, Vandenbroucke, Scott, & Egger, 2008).

Table 2. Studies of breast cancer risk in women with diabetes compared with women without diabetes.

Study	Design	Country	Period	Patients	Main results
Franceschi et al. 1990	Hospital-based case-control	Italy	1983–1994	2,663 breast cancers	OR* 1.0 (95% CI 0.80–1.3)
Sellers et al. 1994	Prospective cohort	USA	1986–1991	Cohort size 41,837, 611 breast cancers	RR* 0.96 (95% CI 0.68–1.36)
Talamini et al. 1997	Multicentric case-control	Italy	1991–1994	2,569 breast cancers	OR* 1.4 (95% CI 1.00–1.80)
Wideroff et al. 1997	Register-based cohort	Denmark	1977–1993	Cohort size 109,581, 777 breast cancers	SIR 1.1 (95% CI 1.10–1.20)
Weiss et al. 1999	Population-based case-control	USA	1990–1992	2,173 breast cancers	RR* 1.13 (95% CI 0.70–1.90)
Baron et al. 2001	Population-based case-control	USA	1990–1994	5,669 breast cancers	OR* 1.2 (95% CI 1.00–1.40)
Mink et al. 2002	Cohort	USA	1987–1995	Cohort size 7,894, 187 breast cancers	RR* 1.39 (95% CI 0.86–2.23)
Michels et al. 2003	Cohort	USA	1976–1998	Cohort size 116,488, breast cancers 5,189	HR 1.17 (95% CI 1.01–1.35)
Jee et al. 2005	Cohort	Korea	1992–2002	Cohort size 468,615	HR 1.51 (95% CI 1.26–1.80)

OR = odds ratio, SIR = standardised incidence ratio, HR = hazard ratio, CI = confidence interval

*Reported ORs and RRs are more likely to be HRs based on the study designs (Knol et al., 2008).

2.1.4 Association with cancer prognosis

In a recent Scottish study, cancer was seen to have overtaken cardiovascular diseases and become the leading cause of death in patients with T2D as a result of more aggressive cardiovascular treatments (Collier, Meney, Hair, Cameron, & Boyle, 2019). Especially in women with T2D, mortality from cancer was seen to be increased compared with that in women from the Scottish national population (Collier et al., 2019). However, the duration of T2D did not have an association with death causes (Collier et al., 2019). In contrast, elevated mortality rates from cancer have been reported shortly after T2D diagnosis followed by declining mortality rates during the first three years, then increasing with age and duration of T2D (Huo et al., 2018).

It is estimated that patients with T2D have 25% higher mortality from cancers compared with patients without diabetes (Seshasai, Kaptoge, Thompson, Di Angelantonio, & Sarwar, 2011). Diabetes has been associated with a worse prognosis of cancer generally (Currie et al., 2012; van de Poll-Franse, L. V. et al., 2007). Furthermore, the prognoses of cases of liver, pancreatic, colorectal, lung and bladder cancer are reported to be poorer in patients with T2D (Seshasai et al., 2011).

Worse prognosis among patients with T2D also applies to women with breast cancer (Yancik et al., 2001). In addition, Jee et al. (2005) reported a notably increased mortality from breast cancer in female breast cancer patients with T2D. In a recent Finnish cohort study the risk of death from breast cancer was higher among women with T2D and the risk increased with the duration of T2D (Murto, Artama, Pukkala, Visvanathan, & Murtola, 2018).

Although there are fewer studies on T2D and survival after ovarian cancer, the results suggest that the prognosis of ovarian cancer is worse among women with T2D (Bakhru, Buckanovich, & Griggs, 2011; Shah et al., 2014). Shah et al. (2014) suggested that women with diabetes mellitus (DM) have shorter progression-free survival (PFS) and lower overall survival (OS) than patients without DM, but this result was not verified when the results were adjusted with BMI among other factors. Bakhru et al. (2011) reported lower OS in women with ovarian cancer and T2D but no difference was seen in disease-free survival (DFS). Women with T2D are up to 75% more likely to have significant comorbidity than women without T2D, which might affect the OS (Bakhru et al., 2011). In addition, women with T2D have been reported to be less likely to have been sufficiently surgically staged (Bakhru et al., 2011).

2.1.5 Treatment options in T2D

Patients diagnosed with T2D should be encouraged to make lifestyle changes such as increasing physical activity, reducing weight and eating a healthy diet (Inzucchi et al., 2012). However, pharmacotherapy is recommended as soon as the diagnosis is set (Type 2 diabetes: Current Care Guidelines, 2018). The first-line medical treatment in cases of T2D is usually metformin, and after that, combination with other oral second-line treatment or with insulin if glycaemic targets are not met (Chatterjee et al., 2017). Changes in the use of various types of ADM in Finland over the years are illustrated in Figure 2.

As all ADMs except insulin require at least some degree of residual insulin secretion to work, it is presumable that these oral ADMs are more frequently used in the early stages of T2D than insulin. It is characteristic of T2D that insulin secretion decreases over time, but the rate of decline is variable and not inevitable in all cases (Zangeneh et al., 2006). Chronic hyperglycaemia in T2D causes β-cell malfunction and insulin resistance (Rossetti, Giaccari, & DeFronzo, 1990). Therefore, hyperglycaemia is not only a manifestation of T2D but is also responsible for the condition (Rossetti et al., 1990).

Metformin and its possible anticancer effects

The history of metformin (1,1-dimethylbiguanide hydrochloride) is connected to a traditional herbal medicine, goat's rue (Bailey, 2017) and its glucose-lowering activity was found as early as in 1918 (Watanabe, 1918). In 1957 metformin was introduced to diabetes treatment (Sterne, 1957) and in 1967 it was available in Finland (Finnish Medicines Agency, 2019).

At present, metformin is still the first-line medical treatment for T2D (Flory & Lipska, 2019). It is usually well-tolerated and has only a few contraindications, for example renal dysfunction (Chatterjee et al., 2017).

Metformin decreases hepatic glucose outlay, increases peripheral tissue sensitivity and stimulates glucagon-like peptide-1 agonist (GLP-1) secretion. In addition, metformin is weight-neutral, it lowers HbA1C concentrations and does not cause hypoglycaemia (Chatterjee et al., 2017).

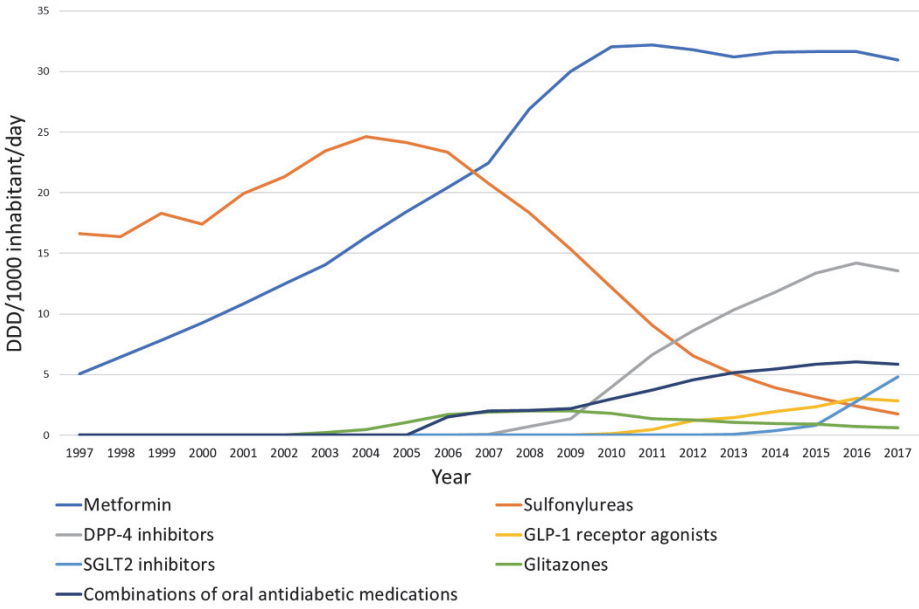

Fig. 2. Trends in the use of metformin (DDD 2 g), sulfonylureas (DDD 7 mg), DPP-4 inhibitors (DDD 0.1 g), GLP-1 receptor agonists (exenatide DDD 15 µg, liraglutide DDD 1.2 mg), SGLT2 inhibitors (dapagliflozin DDD 10 mg, empagliflozin DDD 17.5 mg) and glitazone (rosiglitazone DDD 6 mg, pioglitazone DDD 30 mg) in Finland in 1997–2017 (Finnish Medicines Agency Fimea & Social Insurance Institution, 1999; 2001; 2003; 2006; 2009; 2012; 2014; 2018).

Metformin has been shown to have anti-mitotic, anti-angiogenic and anti-inflammatory effects (Gadducci et al., 2016). AMP-activated protein kinase (AMPK) is the main signalling route (Aljada & Mousa, 2012; Patel, Kumar, & Singh, 2015) (Figure 3). It inhibits the growth of ovarian cancer cells in a time- and dose-dependent manner and this inhibition is also seen in platinum-resistant cell lines (Rattan, Giri, Hartmann, & Shridhar, 2011). It also seems to decrease both proliferation and angiogenesis and in addition potentiates the cytotoxic effect of cisplatin in ovarian cancer cells (Shank et al., 2012). Also, metformin-treated mice develop smaller ovarian tumours and have fewer metastatic nodules than controls (Rattan et al., 2011).

Metformin enhances cytotoxicity in combination with chemotherapy and increases radiosensitivity in breast-cancer cells (Rizos & Elisaf, 2013) and in *in vitro* studies it has inhibited breast-cancer cell growth. It has also been reported that increasing concentrations of metformin have led to extended growth inhibition in a

linear fashion (Zakikhani, Blouin, Piura, & Pollak, 2010) and have reduced the levels of mammalian target of rapamycin (mTOR) indirectly via AMPK in breast-cancer cells (Zakikhani et al., 2010) (Figure 3). In addition, metformin seems to decrease cellular proliferation, reduce colony formation and induce partial cell-cycle arrest (G[1] checkpoint) in breast-cancer cells (Alimova et al., 2009).

Sulfonylureas

The action of sulfonylureas, such as gliclazide and glimepiride, are based on the stimulation of insulin secretion by pancreatic β-cells (Chatterjee et al., 2017). However, sulfonylureas are associated with hypoglycaemia, weight gain and adverse cardiovascular events (Abdelmoneim et al., 2015; Thule & Umpierrez, 2014). In a meta-analysis conducted by Chen et al. (2017), sulfonylureas seemed to be associated with a higher cancer risk compared with metformin.

Dipeptidyl peptidase-4 (DPP-4) inhibitors

DPP-4 inhibitors (gliptins), for example sitagliptin and vildagliptin, increase insulin secretion and decrease glucagon secretion by increasing postprandial active incretin concentrations (Inzucchi et al., 2012). DPP-4 inhibitors are associated with good tolerability in chronic renal failure, a mild risk of hypoglycaemia, and weight neutrality (Coppolino et al., 2018). However, the use of DPP-4 inhibitors has been linked to modest HbA1c decreases, urticaria and angioedema (Inzucchi et al., 2012). Recent studies indicate that DPP-4 inhibitors might also have anti-tumoral effects (Almagthali et al., 2019).

GLP-1 receptor agonists

GLP-1 receptor agonists, for example liraglutide, activate GLP-1 receptors, which leads to increased insulin secretion, decreased glucose secretion and slows gastric emptying (Inzucchi et al., 2012). GLP-1 receptor agonists reduce weight and do not cause hypoglycaemia (Inzucchi et al., 2012). They are suggested to be initiated among those patients with T2D who are at an elevated risk of cardiovascular events (Marso, Bain et al., 2016; Marso, Daniels et al., 2016) or are overweight (Astrup et al., 2009).

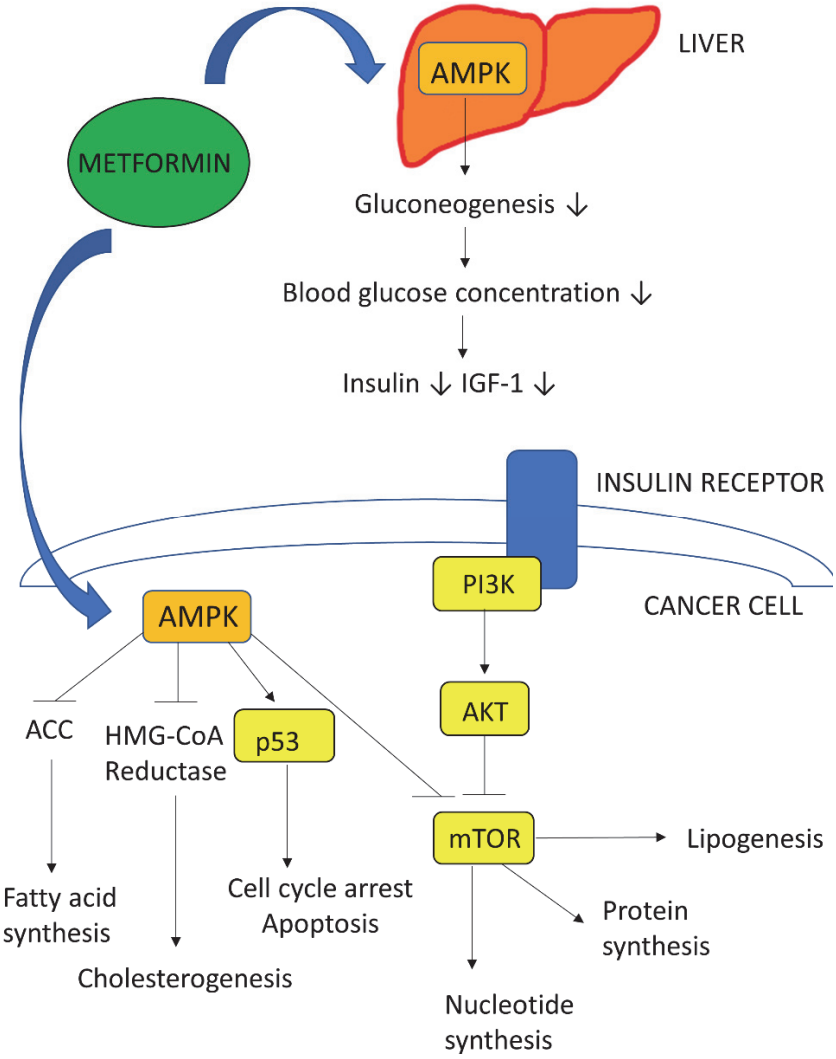

Fig. 3. Metformin affects cancer cells both directly and indirectly. It activates AMP-activated protein kinase (AMPK), which leads, among other things, to inhibition of mammalian target of rapamycin (mTOR). It also sensitises tissues to insulin, reduces hepatic gluconeogenesis and decreases circulating insulin levels. This leads indirectly to reduced phosphatidylinositol-3-kinase (PI3K) signalling. IGF-1 = insulin-like growth factor 1, ACC = acetyl-CoA carboxylase, HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A, p53 = tumour protein p53, AKT = serine/theonine-specific protein kinase. Modified after Dowling et al. (2011) and Sosnicki et al. (2016).

When liraglutide was studied in regard to weight loss among persons without T2D, increased incidences of both malignant and pre-malignant breast neoplasms were reported, although the incidence of neoplasms in general was similar to that in the placebo group (Pi-Sunyer et al., 2015). However, epidemiological studies have not reported an association between the use of GLP-1 receptor agonists and breast cancer incidence (Funch et al., 2018; Hicks et al., 2016).

SGLT2 (sodium-glucose co-transporter 2) inhibitors

SGLT2 inhibitors, dapagliflozin and empagliflozin, inhibit renal glucose absorption in an insulin-dependent manner by inhibiting SGLT2, which is a protein located in the proximal tubule of the kidney and is mainly responsible for reabsorption of glomerular-filtered glucose (List, Woo, Morales, Tang, & Fiedorek, 2009). SGLT2 inhibitors lower HbA1c levels effectively, improve weight control, lower systolic blood pressure and reduce fasting plasma glucose levels (Bailey, Gross, Pieters, Bastien, & List, 2010). Problems related to SGLT2 inhibitors are genital and urinary infections and euglycaemic diabetic ketoacidosis (Clar, Gill, Court, & Waugh, 2012; Peters et al., 2015).

SGLT2 inhibitors have not been reported to be associated with an increased risk of cancer overall (H. Tang et al., 2017). An increased risk of bladder cancer has been reported among SGLT2 inhibitor users (H. Tang et al., 2017), but the evidence is not robust (Ptaszynska et al., 2015). On the other hand, a lower incidence of gastrointestinal cancer has also been reported (H. Tang et al., 2017).

Glitazones

Glitazones (thiazolidinediones), for example pioglitazone, increase insulin sensitivity in the liver and adipose tissue (Yki-Järvinen, 2004). Glitazones are not associated with hypoglycaemia but are related to weight gain, bone fractures, oedema and heart failure (Inzucchi et al., 2012).

Long-term use of pioglitazone has been associated with bladder-cancer risk (Lewis et al., 2011; Tuccori et al., 2016) but this association has not been corroborated in all studies (Erdmann, Harding, Lam, & Perez, 2016; Lewis et al., 2015).

Insulin

Insulins increase glucose disposal and decrease hepatic glucose production by activating insulin receptors (Inzucchi et al., 2012). It is recommended to add insulin to the treatment of T2D if hyperglycaemia is not otherwise managed or there are signs of insulin deficiency (Type 2 diabetes: Current Care Guidelines, 2018). Insulin is universally effective, and the efficacy is theoretically unlimited (Inzucchi et al., 2012). The major side-effects of insulin are hypoglycaemia and weight gain (Inzucchi et al., 2012).

Insulin therapy might be associated with an elevated cancer risk (Currie, Poole, & Gale, 2009). In some studies, the rise of cancer has not been found to differ between insulin types (Blin et al., 2012; Fagot et al., 2013; Grimaldi-Bensouda et al., 2014; Ljung et al., 2011). However, long-acting insulin analogues (glargine and detemir) and their high-level propensity to bind IGF-1 receptors are linked to both cancer-cell proliferation and protection against apoptosis in *in vitro* and *in vivo* studies (Kurtzhals et al., 2000; Yehezkel et al., 2010). Additionally, the increased cancer risk has mainly been linked to the insulin glargine in some epidemiological studies (Hemkens et al., 2009; Mannucci et al., 2010), but in some studies the increased risk has only been seen in some cancer types, for example, in breast cancer (Colhoun, 2009; Jonasson et al., 2009; Ruiter et al., 2012) at least when glargine use is long-term (Habel et al., 2013). In contrast to this, there are also studies which have not found an association between glargine use and breast cancer (Suissa et al., 2011). Also, the European Medicines Agency stated in 2013 that cancer risk is not increased among glargine users (European Medicines Agency, 2013).

2.1.6 Association between T2D and cardiovascular diseases

Type 2 diabetes is a risk factor of coronary heart disease mortality and morbidity (Kuusisto, Mykkänen, Pyörälä, & Laakso, 1994). Glycaemic control decreases coronary events (Ray et al., 2009) but very intense glycaemic control increases mortality and does not reduce cardiovascular events (Gerstein et al., 2008).

Cardiovascular risk factors, which include obesity, hypertension, dyslipidaemia, smoking, family history, chronic kidney disease and albuminuria, should be systemically assessed in patients with diabetes. Patients with T2D have an increased risk of lipid abnormalities. Lifestyle changes such as weight loss, nutrition therapy and increased physical activity should be recommended to all

patients with T2D to reduce the risk of cardiovascular diseases (American Diabetes Association, 2019).

Obviously, high serum cholesterol levels increase mortality from coronary heart disease, but the association between hypercholesterolaemia and mortality from cancers depends on cancer type, as in some cancers hypercholesterolaemia is linked to increased mortality, while in other cancers, it is linked to decreased mortality (Neaton et al., 1992). As early reports suggested that high cholesterol levels might be beneficial as regards cancer prevention, debate on the use of cholesterol-lowering medications in prevention of coronary heart disease at the expense of increased cancer risk, began (Goldstein & Mascitelli, 2009). However, it seems that the decreased cancer risk associated with high cholesterol levels is short-term and might be explained by preclinical effects of cancer on cholesterol levels (Strasak et al., 2009).

In Finnish guidelines, the level of low-density lipoprotein (LDL) in plasma is recommended to be less than 2.5 mmol/l in patients with T2D regardless of other risk factors and less than 1.8 mmol/l in those patients with coincident coronary heart disease, cerebral arterial disease or peripheral arterial disease (Type 2 diabetes: Current Care Guidelines, 2018). If the targets are not met otherwise, statin therapy is recommended to be initiated (Type 2 diabetes: Current Care Guidelines, 2018). In Finland, 79% of patients with newly diagnosed diabetes have been found to use statins for secondary prevention and 40% for primary prevention of cardiovascular diseases (Vehko et al., 2013).

Statins can be divided into lipophilic (e.g. simvastatin, atorvastatin, fluvastatin, lovastatin) and hydrophilic (e.g. rosuvastatin, pravastatin) types on the basis of their liposolubility properties (Bytyci et al., 2017). It seems that lipophilic and hydrophilic statins have similar efficacy and safety in patients with coronary artery disease (Bytyci et al., 2017). However, the possible association with decreased cancer incidence is mainly linked to lipophilic statins (Farwell et al., 2008). The apparently favourable effect of lipophilic statins on cancer prognosis is mainly explained by differences in cell-membrane penetration, as lipophilic statins diffuse across the membrane easily while hydrophilic statins rely on active transport (Beckwitt, Shiraha, & Wells, 2018).

Statins inhibit mevalonate metabolism and their anti-tumour assets are derived from this. The mevalonate pathway (Figure 4) produces biologically active metabolites which have roles in tumour-cell proliferation, survival, invasion and metastasis (Thurnher, Nussbaumer, & Gruenbacher, 2012). Mutant p53, which is seen in the majority of cancers, upregulates the mevalonate pathway and this

finding supports the anti-cancer role of statins (Thurnher et al., 2012). In addition, favourable effects of statins on p53 and Akt signalling have been found (Roudier, Mistafa, & Stenius, 2006) (Figure 5).

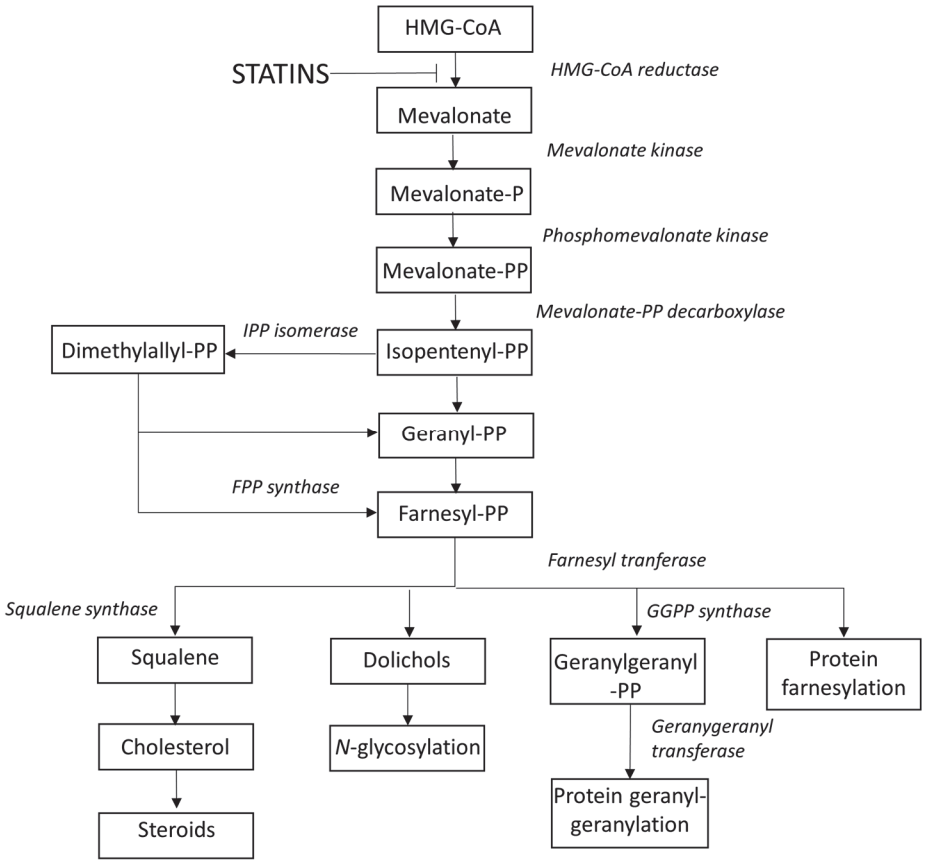

Fig. 4. In the mevalonate pathway, which is inhibited by statins, HMG-CoA reductase converts HMG-CoA to mevalonate which is metabolised to isopentenyl-PP and dimethylallyl-PP. Due to the action of FPP synthase, farnesyl-PP is formed from dimethylallyl-PP. Geranylgeranyl pyrophosphate (GGPP) results from the action of GGPP synthase. Cholesterol, steroids and dolichols are products of the mevalonate pathway. HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A, PP = pyrophosphate. Modified from Thurnher et al. (2012).

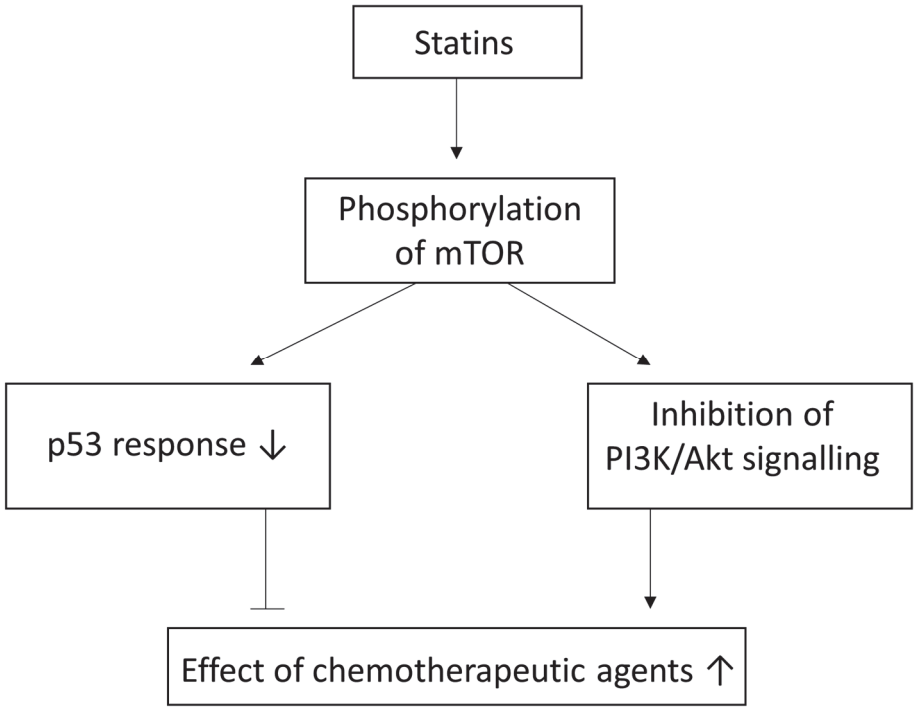

Fig. 5. The effect of statins on chemotherapeutic agents via p53 and Akt signalling. Modified after Roudier, Mistafa & Stenius (2006).

2.2 Ovarian cancer

It has been estimated that in 2018 there were approximately 300,000 new ovarian cancer cases worldwide, covering 3─4% of all cancer cases in women. The estimated number of ovarian cancer deaths was 180,000 in 2018 (Ferlay et al., 2019).

Epithelial ovarian cancer is the most common malignancy (90%) in the ovaries, and histologically it includes both high- (70%) and low-grade (less than 5%) serous carcinomas, endometrioid carcinomas (10%), clear cell carcinomas (10%), mucinous carcinomas (3%), malignant Brenner tumours, seromucinous carcinomas and undifferentiated carcinomas (Kurman, Carcangiu, Young, & Herrington, 2014; Prat, 2014).

High-grade serous epithelial ovarian carcinoma, fallopian tubal and peritoneal carcinomas share similar clinical behaviour and treatment and therefore are held as a single entity (Prat, 2014).

The ovarian surface mesothelium was previously considered as the primary source of serous carcinomas, with Müllerian metaplastic change to the tubal epithelial type and/or cortical inclusion cysts (Kurman et al., 2014). Current understanding suggests the fallopian tube as the origin of high-grade serous carcinoma (Medeiros et al., 2006). Serous tubal intraepithelial carcinoma (STIC) is present in the fallopian tubes in up to 60% of women with high-grade serous carcinomas and STIC have similar features as high-grade serous carcinomas such as aberrant p53 protein expression, high proliferation indices and marked genomic instability (Kurman et al., 2014). Mucinous carcinomas, which are composed of gastrointestinal-type cells containing intra-cytoplasmic mucin, usually develop from mucinous borderline tumours, although a minority can arise from a teratoma or a Brenner tumour (Kurman et al., 2014). Malignant Brenner tumours are reminiscent of an invasive urothelial carcinomas (Kurman et al., 2014).

Ovarian cancer is categorised as advanced when the FIGO stage is ≥ III, i.e. the tumour has spread to the peritoneum outside the pelvis and/or show metastasis in the retroperitoneal lymph nodes (Prat, 2014). As a result of non-specific symptoms, i.e. abdominal pain and distension, ovarian cancer is usually diagnosed at an advanced stage in most patients (Cannistra, 1993). Unfortunately, no screening tools implementable into national programmes (Gupta, Gupta, & Naumann, 2019), even tools to screen women with a high-risk of ovarian cancer (Fishman et al., 2005) have been found despite an enormous amount of research.

The prognosis of ovarian cancer is poor with 5-year relative survival in the Nordic countries varying from 40 to 50% (Nordcan, 2019). Increasing age, residual tumour after surgery, tumour stage and histology are all independent predictors of prognosis (Winter et al., 2007).

The golden standard for ovarian cancer treatment is surgery and platinum-based chemotherapy. Complete resection of all macroscopic disease has been shown to be the most important independent prognostic factor in ovarian cancer. If primary surgery with no macroscopic visible disease is not achievable, neoadjuvant chemotherapy should be initiated. Adjuvant chemotherapy should be offered to almost all patients after operation with a few exceptions (stage IA low-grade serous, grade 1-2 endometrioid or grade 1-2 mucinous ovarian cancers). Three-weekly carboplatin-paclitaxel chemotherapy is the standard-of-care in first-line ovarian cancer treatment. Treatment with bevacizumab is the first targeted therapy for

ovarian cancer and it can be used in several treatment lines and also in neoadjuvant treatment combined with chemotherapy. Poly ADP ribose polymerase (PARP) inhibitors have the greatest effect in patients with BRCA1/2 mutations in maintenance treatment of ovarian cancer in both first- and second-line treatment. Therefore, testing for breast cancer susceptibility gene 1 (BRCA1) and 2 (BRCA2) mutations is recommended for all patients with non-mucinous epithelial ovarian cancer (Colombo et al., 2019).

2.2.1 Risk factors and protective factors

Several risk factors and some protective factors have been identified in connection with ovarian cancer. Reproductive factors are associated with ovarian cancer incidence. Nulliparity and older age (over 35 years) at first child birth are considered to increase the risk of ovarian cancer (Negri et al., 1991). Early menarche and late menopause are considered to increase the risk (La Vecchia, 2017). On the other hand, multiparity (Negri et al., 1991) and the use of oral contraceptives (Royar, Becher, & Chang-Claude, 2001) decrease the risk of ovarian cancer. Breastfeeding also seems to lower ovarian cancer risk (Luan et al., 2013).

Endometriosis is associated with an increased risk of ovarian cancer, at least in cases of endometrioid and clear-cell histologies (Mogensen, Kjaer, Mellemkjaer, & Jensen, 2016). The role of PCOS as a risk factor of ovarian cancer is not clear (Harris & Terry, 2016). Tubal ligation and salpingectomy reduce the risk of ovarian cancer, especially that with endometrioid histology (Madsen, Baandrup, Dehlendorff, & Kjaer, 2015).

Familial clustering in ovarian cancer has also been observed. Some specific genes have been identified and the best-known predisposing gene mutations are in BRCA1 and BRCA2 (Easton, Ford, & Bishop, 1995; Ford et al., 1998). Also, in Lynch syndrome, gene mutations in MLH1 (MutL homolog 1), MSH2 (DNA mismatch repair protein, MutS protein homolog 2) and MSH6 (MutS homolog protein 6), increase the risk of ovarian cancer (Helder-Woolderink et al., 2016; H. T. Lynch, Fitzsimmons, Conway, Bewtra, & Lynch, 1990; Malander et al., 2006). In addition, mutations in the tumour suppressor gene p53, and genes which are involved in the double-strand-breaks repair system, CHEK2 (checkpoint kinase 2), RAD51, BRIP1 (BRCA1-interacting protein 1) and PALB2 (partner and localizer of BRCA2) are associated with hereditary ovarian cancers (Toss et al., 2015).

2.2.2 Metformin and ovarian cancer

There are only two studies that have been focused on the incidence of ovarian cancer in metformin users, as seen in Table 3 (Bodmer et al., 2011; Tseng, 2015). In the study by Tseng (2015), a lower incidence of ovarian cancer was reported in women with T2D who were metformin ever-users compared with never-users. In the study by Bodmer (2011), only a long-term metformin use seemed to have an association with a lower incidence of ovarian cancer. However, in studies which have reported the incidence of all cancers, when ovarian cancer cases were extracted, no association was found between metformin use and ovarian cancer incidence (Baur et al., 2011; P. D. Home et al., 2010).

A few studies have reported a better prognosis of ovarian cancer in metformin users (Bar et al., 2016; Kumar et al., 2013) but in one study, favourable results were limited only to progression-free survival and not seen in overall survival (Romero et al., 2012). The most recent study on ovarian cancer prognosis did not find an association between metformin use and overall survival (Garcia et al., 2017).

2.2.3 Statins and ovarian cancer

Elevated levels of LDL *per se* have been linked to worse prognosis of ovarian cancer (A. J. Li et al., 2010). A meta-analysis by Liu et al. (2014) reported a lower risk of ovarian cancer in statin users and the association was stronger if statin use had lasted more than five years.

In epidemiological studies concentrating on ovarian cancer, an association between statin use and ovarian cancer risk has not been found in the majority (Baandrup, Dehlendorff, Friis, Olsen, & Kjaer, 2015; Lavie, Pinchev, Rennert, Segev, & Rennert, 2013; Yu, Boudreau, Buist, & Miglioretti, 2009). However, one study has reported an increased incidence of ovarian cancer in users of hydrophilic statins (Desai et al., 2018) and Akinwunmi et al. (2019) reported a decreased risk of ovarian cancer in users of lipophilic statins (Table 4).

In a meta-analysis by Li & Zhou (2018) it was concluded that post-diagnostic statin use is associated with better prognosis in ovarian cancer. Similarly, some individual studies have reported a better prognosis in ovarian cancer patients who use statins (Couttenier et al., 2017; Elmore, Ioffe, Scoles, Karlan, & Li, 2008; Lavie et al., 2013; Vogel, Goodman, Li, & Jeon, 2017). However, there are also studies where no association between statin use and ovarian cancer survival has been found (Bar et al., 2016; Habis et al., 2014; Verdoodt et al., 2017) (Table 5).

Table 3. Incidence and prognosis of ovarian cancer among metformin users in women with type 2 diabetes.

Study	Design	Country	Period	Outcome measure	Patients	Reference group	Main results
Bodmer et al. 2011	Register-based case-control	UK	1995–2009	Incidence	1,611 ovarian cancers of which 85 were in women with T2D and 41 in metformin users	Women with T2D and no prior metformin use	OR* 0.38 (95% CI 0.10–0.94) in long-term (≥ 30 prescriptions) metformin users
Tseng et al. 2015	Register-based cohort	Taiwan	1998–2009	Incidence	Cohort size 479,475, 3,201 ovarian cancers of which 601 were in metformin users	Women with T2D and no use of metformin	aHR 0.66 (95% CI 0.59–0.73)
Romero et al. 2012	Hospital-based cohort	USA	1992–2010	Prognosis	341 ovarian cancers of which 44 were in women with T2D and 16 in metformin users	Women with T2D without metformin use	PFS: HR 0.38 (95% CI 0.16–0.90), OS: HR 0.43 (95% CI 0.16–1.19)
Kumar et al. 2013	Hospital-based cohort	USA	1995–2010	Prognosis	239 ovarian cancers of which 103 were in women with T2D and 61 in metformin users	Women without metformin use, also including women without T2D	OS: HR 0.45 (95% CI 0.26–0.83)
Bar et al. 2016	Hospital-based cohort	Israel	2000–2012	Prognosis	143 ovarian cancers of which 22 were in women with T2D and 12 in metformin users	Women with T2D without metformin use	RFS: HR 0.14 (95% CI 0.00–0.52)
Garcia et al. 2017	Register-based cohort and nested case-control	USA	2007–2011	Prognosis	2,291 ovarian cancers of which 552 were in women with T2D and 172 in metformin users	Women without metformin use, also including women without T2D	OS: HR 0.96 (95% CI 0.75–1.23)

aHR = adjusted hazard ratio, PFS = progression-free survival, OS = overall survival, RFS = recurrence-free survival, T2D = type 2 diabetes

* The reported OR is more likely to be an HR according to study design (Knol et al., 2008).

Table 4. Studies of ovarian cancer incidence in statin users compared with non-statin users.

Study	Design	Country	Period	Patients	Main results
Yu et al. 2009	Cohort	USA	1990–2004	Cohort size 93,619; 326 ovarian cancer cases of which 12 in statin users	HR 0.69 (95% CI 0.32–1.49)
Lavie et al. 2013	Hospital-based case-control	Israel	2003–2010	126 ovarian cancers of which 38 in statin users	OR* 0.54 (95% CI 0.26–1.13)
Baandrup et al. 2015	Register-based case-control	Denmark	2000–2011	4,103 ovarian cancers of which 434 in statin users	OR* 0.98 (95% CI 0.87–1.10)
Desai et al. 2018	Cohort	USA	1993–1998	Cohort size 161,808; 763 ovarian cancers of which 62 in statin users	aHR 1.15 (95% CI 0.89–1.50), in hydrophilic statin users HR 1.72 (95% CI 1.15–2.56)
Akinwunmi et al. 2019	Case-control	USA	1992–2008	2,040 epithelial ovarian cancers of which 188 in statin users	In lipophilic statin users OR* 0.68 (95% CI 0.54–0.85)

HR = hazard ratio, CI = confidence interval OR = odds ratio

* Reported ORs are more likely to be HRs based on study designs (Knol et al., 2008).

Table 5. Studies of ovarian cancer survival in relation to statin use.

Study	Design	Country	Period	Patients	Reference group	Main results
Elmore et al. 2008	Hospital-based cohort	USA	1996–2001	126 ovarian cancers of which 17 in statin users	Statin never-users	OS: HR 0.45 (95% CI 0.23–0.88)
Lavie et al. 2013	Cohort	Israel	2003–2010	150 ovarian cancers of which 67 in statin users	Patients who had never used statins or used them only before diagnosis or both before and after diagnosis	Statin use only after diagnosis (n = 16) DSM: HR 0.47 (95% CI 0.26–0.85)
Habis et al. 2014	Single-institution cohort	USA	1992–2013	442 ovarian cancers of which 68 in statin users	Patients with hyperlipidaemia treated with statins compared with patients without hyperlipidaemia	PFS: HR 0.84 (95% CI 0.56–1.27), DSM: HR 0.80 (95% CI 0.50–1.29)
Bar et al. 2016	Hospital-based cohort	Israel	2000–2012	143 ovarian cancers of which 43 in statin users	No statin use following cancer diagnosis	Multivariate RFS: HR 0.66 (95% CI 0.40–1.08)
Couttenier et al. 2017	Register-based cohort	Belgium	2004–2012	5,416 ovarian cancers of which 1,255 in women with at least one statin prescription after diagnosis	Patients without statin prescription	OS: HR 0.81 (95% CI 0.72–0.90)
Vogel et al. 2017	Register-based cohort	USA	2007–2009	1,431 ovarian cancers of which 609 in statin users	Patients without statin use	Lipophilic statin OS: HR 0.65 (95% CI 0.53–0.79)
Verdoodt et al. 2017	Register-based cohort	Denmark	2000–2013	4,419 ovarian cancers of which 476 in statin users	Patients without statin use	Post-diagnostic statin use OS: HR 0.90 (95% CI 0.78–1.04), DSM: HR 0.90 (95% CI 0.76–1.08)

PFS = progression-free survival, DSM = disease-specific mortality, RFS = recurrence-free survival, OS = overall survival

2.3 Breast cancer

Breast cancer is the most common cancer in women worldwide; it represents 24% of all new cancer cases. It has been estimated that in 2018, over two million new breast-cancer cases were diagnosed globally, and 600,000 women died of the disease (Ferlay et al., 2019).

In the past, a large population (40─75%) of breast cancers were histologically labelled as invasive ductal carcinomas but now the recommended term is invasive carcinoma of no special type (Lakhani, Ellis, Schnitt, Tan, & van de Vijver, 2012). The second largest histological entity is invasive lobular carcinoma which represents approximately 5 to 15% of breast cancers (Ingle, Katkade, Chavan, & Girji, 2016; Lakhani et al., 2012).

The previous term, invasive ductal carcinoma, resulted from the incorrect impression that these tumours are derived from mammary ductal epithelium, whereas invasive lobular carcinomas were thought to arise from within the lobules (Lakhani et al., 2012). The origin of breast cancer is the epithelial compartment of glandular breast tissue (Fentiman & D'Arrigo, 2004). A precursor of invasive carcinoma is *in situ* carcinoma, which is restricted to the epithelial compartment, while invasive carcinoma intrudes into the basement membrane of the epithelium and infiltrates to connective breast tissue (Fentiman & D'Arrigo, 2004). There are two types of *in situ* lesions, ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS), which despite their histological features can be found as precursors of both invasive carcinoma of no special type, and lobular carcinomas (Fentiman & D'Arrigo, 2004; Lakhani et al., 2012). DCIS has a greater risk of developing into invasive carcinoma than LCIS, and therefore DCIS is usually treated after detection, while discovery of LCIS often leads to surveillance only (Fentiman & D'Arrigo, 2004).

Tumour-Node-Metastasis (TNM) is the most widely used system for staging breast cancer (Brierley, Gospodarowicz, & Wittekind, 2017; Cserni, Chmielik, Cserni, & Tot, 2018; Lakhani et al., 2012). T concerns tumour size (T1─4), N concerns for involvement of lymph nodes (N0─3) and M, distant metastases (M0─1) (Brierley et al., 2017; Denoix, 1944).

Both tumour size and lymph node involvement are independent predictors of poor prognosis of breast cancer (Carter, Allen, & Henson, 1989). The presence of distant metastasis is also associated with poor prognosis (Falkson et al., 1995). However, micrometastases (size less than 0.2 cm or ≥200 cells in a single nodal cross-section) or isolated tumour clusters (size less than 0.02 cm or <200 cells in

single nodal cross-section) seem to have no influence on prognosis (Lakhani et al., 2012). The most important single prognostic factor is axillary lymph-node status (Lakhani et al., 2012). In addition, tumour histology (C. I. Li, Moe, & Daling, 2003) and grade (Elston & Ellis, 1991; Rakha et al., 2008) have an impact on breast-cancer prognosis. Grading of breast cancer into grades 1 to 3 is based on the percentage of tubule formation, the degree of nuclear pleomorphism and an exact mitotic count by using a defined field area (Elston & Ellis, 1991). In addition, the presence of lymph-vascular invasion is an independent marker of poorer prognosis in breast cancer (Lakhani et al., 2012; Pinder et al., 1994). The prognosis of multifocal breast-cancer tumours is disputable; in some studies it has been considered as an independent risk factor of worse prognosis (Weissenbacher et al., 2010), but in other studies this has not been confirmed (S. P. Lynch et al., 2012).

Early breast cancer can be treated either by mastectomy (large tumours) or breast-conserving surgery followed by irradiation. Sentinel-lymph-node mapping or axillary-node dissection is part of surgical treatment. In some cases, neoadjuvant chemotherapy is used prior to surgery to reduce the size of the tumour. Irradiation, including regional lymph-node irradiation, is initiated after mastectomy for women with an intermediate or high risk of recurrence, for example if metastasis is present in axillary lymph nodes or the tumour has invaded to the skin. Adjuvant therapy after surgery is individualised. In women with a low risk of recurrence, surgery is sufficient in some cases, but others require hormonal therapy. Women with an intermediate recurrence risk are treated with adjuvant hormonal treatment with or without preceding chemotherapy, depending on tumour grade and hormone receptor status. Women with a high recurrence risk are treated after surgery with chemotherapy combined with hormonal treatment or trastuzumab depending on hormone receptor and HER2 (human epidermal growth factor receptor 2) status. In the majority of patients with triple-negative breast cancer, anthracycline- and taxane-based chemotherapy is preferred, but alkylating chemotherapy should be considered in BRCA1- and BRCA2- associated cancers. Paclitaxel combined with trastuzumab is sufficient in stage I HER2-positive cancer, but in more advanced stages, anthracycline followed by taxane and trastuzumab should be initiated (Curigliano et al., 2017).

2.3.1 Risk factors and protective factors

Several risk factors and protective factors for breast cancer have been identified. Reproductive factors seem to play an essential role in the development of breast

cancer. Early menarche, late menopause, late age at first pregnancy, nulliparity and late menopause seem to increase the risk of breast cancer (Cole & MacMahon, 1969; Kelsey, Gammon, & John, 1993). On the other hand, longer duration of breastfeeding has been observed to reduce the risk (Chang-Claude, Eby, Kiechle, Bastert, & Becher, 2000).

Postmenopausal hormone replacement therapy (HRT) is known to increase the risk of breast cancer (Writing Group for the Women's Health Initiative Investigators, 2002). In addition, the use of hormonal contraceptives slightly increases the risk of breast cancer (Morch et al., 2017).

Nutritional factors also play a role in the development of breast cancer; meat consumption, saturated animal fat, and high intakes of sugar and alcohol are associated with an increased risk of breast cancer, while high intakes of fruit, vegetables, fibre and omega-3 fatty acids are reported to lower the risk (Glade, 1999; Seiler, Chen, Brown, & Fagundes, 2018). Obesity is a major risk factor of breast cancer (Neuhouser et al., 2015; Seiler et al., 2018) and physical activity has been observed to reduce the risk (Kyu et al., 2016).

The environment *in utero* also seems to have a role in the development of breast cancer. Higher birth-weight is associated with an increased risk of breast cancer (Michels et al., 1996). Twinship is also a risk factor of breast cancer, especially in female dizygotic twins (Cerhan et al., 2000). On the other hand, a reduced risk of breast cancer is seen in women whose mothers had toxaemia in pregnancy (Ekbom, Hsieh, Lipworth, Adami, & Trichopoulos, 1997).

Several genetic mutations are identified which increase the risk of breast cancer. Germline mutation in the BRCA1 gene is the best-known and it is estimated that the cumulative risk of breast cancer before the age of 70 is 87% in BRCA1 gene mutation carriers if preventive mastectomy is not performed (Ford, Easton, Bishop, Narod, & Goldgar, 1994). Other known gene mutations which increase breast cancer risk are in BRCA2, and in the genes for tumour protein p53 (Li─Fraumeni syndrome), phosphatase and tensin homolog (PTEN) (Cowden's syndrome), serine/threonine kinase 11(STK11) (Peutz-Jeghers syndrome), chromodomain helicase DNA binding protein 1 (CDH1) and PALB2 (Lalloo & Evans, 2012).

Some surgical procedures such as salpingo-oophorectomy have been linked to reduced breast cancer risk in fertile women (Helmrich et al., 1983). In addition, prophylactic mastectomy for high-risk women reduced the incidence of breast cancer by 85–100% (Alaofi, Nassif, & Al-Hajeili, 2018).

2.3.2 Prognostic biochemical markers in breast cancer

Oestrogen receptor (ER), progesterone receptor (PR) and HER2 are routinely used prognostic biomarkers in invasive breast cancer (Lakhani et al., 2012). Expression of both ER and PR is generally related to better prognosis of breast cancer (Bardou, Arpino, Elledge, Osborne, & Clark, 2003). In the past, HER2 over-expression was linked to unfavourable prognosis (Slamon et al., 1987), but after the era of trastuzumab, the recombinant monoclonal antibody against HER2, the role of HER2 overexpression is more a therapeutic than a purely prognostic issue (Slamon et al., 2001).

Table 6. Classification of molecular subtypes and association with biomarker staining in immunohistochemistry. Modified after Fragomeni et al. (2018).

Molecular subtype	ER	PR	HER2
Luminal A	positive and/or	positive	negative
Luminal B	positive and/or	positive/negative* or	negative
Luminal B	positive and/or	positive/negative** or	positive
HER2-enriched	negative	negative	positive
Basal-type	negative	negative	negative

* PR < 20% and Ki-67 > 14%

** any PR-positive and any Ki-67

ER = oestrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor 2

Breast cancers can be divided into different molecular subtypes on the basis of gene expression profiles analysed on cDNA microarrays (Perou et al., 2000; Sorlie et al., 2003). Subtype classification has an impact on prognosis (Loi et al., 2007; Voduc et al., 2010). Subtypes are luminal A, luminal B, HER2-enriched and basal-like (Fragomeni et al., 2018; Lakhani et al., 2012; Sorlie et al., 2003). Characteristic of the basal-like subtype is high-level expression of keratins 5, 14 and 17, laminin and fatty acid binding protein 7 and epidermal growth factor receptor (EGFR) (Hsu & Hung, 2016; Sorlie et al., 2001). The HER2-enriched type is characterised by high-level expression of genes in the HER2 amplicon (Sorlie et al., 2001). Luminal subtypes show low to high expression of luminal-specific genes which include ER cluster (Sorlie et al., 2001). The luminal A subtype is the most common (Sorlie et al., 2003) and these tumours have a favourable prognosis (Voduc et al., 2010) whereas the basal-like and HER2-enriched subtypes are linked to the shortest survival times (Sorlie et al., 2001). In addition, BRCA1 mutations are associated

with the basal-type subtype (Sorlie et al., 2003). The association between molecular subtypes and immunohistochemical results is shown in Table 6.

2.3.3 Metformin and breast cancer

Two meta-analyses summarised that metformin use is not associated with the incidence of breast cancer (G. H. Tang et al., 2018; T. Yang, Yang, & Liu, 2015).

Some previous original studies have reported an association between metformin use and a lower incidence of breast cancer (Bosco, Antonsen, Sørensen, Pedersen, & Lash, 2011; Chlebowski et al., 2012; Tseng, 2014), but in one study, the reduced incidence was only observed with long-term metformin use (Bodmer, Meier, Krähenbühl, Jick, & Meier, 2010). In two other studies, such an association was not found (Redaniel, Jeffreys, May, Ben-Shlomo, & Martin, 2012; Soffer et al., 2015) (Table 7).

When focusing on survival in breast cancer, most studies have reported a better prognosis among metformin-treated women with T2D (He et al., 2012; Hou et al., 2013; Kim et al., 2015; Xiao et al., 2014). However, some studies reported an association between metformin use and better prognosis only when assessing all-cause mortality (Calip, Yu, Hoskins, & Boudreau, 2015; Peeters et al., 2013) or long-term (more than two years) metformin use (Vissers et al., 2015). Some studies have not found an association between metformin use and survival in breast-cancer patients (Bayraktar et al., 2012; Lega et al., 2013) (Table 8).

Niraula et al. (2012) reported that in a small patient series of 39 women without T2D, short-term treatment with metformin before breast cancer surgery led to favourable changes in apoptosis and proliferation (using TUNEL assays and assessments of the marker Ki-67) in breast-tumour tissue. Also, in a small case-control study (17 cases and 22 controls), Hadad et al. (2011) observed a decrease in Ki-67 activity in women who used metformin prior to breast cancer surgery. However, in a larger case-control study (100 cases and 100 controls) by Bonanni et al. (2012), this observation was not confirmed.

Table 7. Studies of an association between metformin use and incidence of breast cancer in women with type 2 diabetes.

Study	Design	Country	Period	Patients	Reference group	Main results
Bodmer et al. 2010	Register-based cohort and nested case-control	UK	1994–2005	Cohort size 22,621, 305 breast cancers of which 144 metformin users	Women with T2D and no use of metformin	Long-term metformin users OR* 0.44 (95% CI 0.24–0.82)
Bosco et al. 2011	Register-based case-control	Denmark	1989–2008	4,323 women with T2D, 393 breast cancers of which 96 used metformin at least one year	Women with T2D and no use of metformin	OR* 0.77 (95% CI 0.61–0.99)
Chlebowski et al. 2012	Cohort	USA	–2005	Cohort size 68,019 of which 3,401 women with DM. 347 breast cancers in women with DM of which 104 in metformin users	Women without DM	HR 0.75 (95% CI 0.57–0.99)
Redaniel et al. 2012	Register-based cohort	UK	1987–2007	52,657 women with T2D, 873 breast cancers of which 151 in patients who used only metformin	Patients who used only sulfonylurea	HR 1.04 (0.79–1-37)
Tseng 2014	Register-based cohort	Taiwan	1998–2009	476,282 women with T2D, 11,734 breast cancers of which 2,412 in metformin users	Never-users of metformin	HR 0.63 (95% CI 0.60–0.67)
Soffer et al. 2015	Cohort	USA	1998–2009	66,788 women with T2D, 1,572 breast cancers of which 143 in patients who used only metformin	Patients who used non-metformin drugs	Only metformin users HR 1.12 (95 % CI 0.92–1.35)

OR = odds ratio, CI = confidence interval, HR = hazard ratio, DM = diabetes mellitus, T2D = type 2 diabetes

* Reported ORs are more likely to be HRs based on the study designs (Knol et al., 2008).

Table 8. Studies on breast cancer survival in relation to metformin use in women with type 2 diabetes.

Study	Design	Country	Period	Patients	Reference group	Main results
He et al. 2012	Hospital-based cohort	USA	1998–2010	Cohort size 1,984, 154 breast cancer patients with T2D of which 88 metformin users	Women with T2D and no use of metformin	OS: HR 0.52 (95% CI 0.28–0.97), BCSM: HR 0.47(95% CI 0.24–0.90)
Lega et al. 2013	Population-based cohort	Canada	1997–2008	Cohort size 2,361 breast-cancer patients with T2D of which 1,094 metformin users	Women with T2D and no use of metformin	OS: HR 0.97 (95% CI 0.92–1.02), BCSM: HR 0.91 (95% CI 0.81–1.03)
Peeters et al. 2013	Register-based cohort	Denmark	1996–2008	1,058 breast-cancer patients with T2D of which 508 metformin users	Non-metformin-treated women with T2D	OS: HR 0.74 (95% CI 0.58–0.96), DSM: HR 0.88 (95% CI 0.59–1.29)
Hou et al. 2013	Hospital-based cohort	China	2002–2006	5,634 breast cancers of which 1,013 in women with T2D and 419 used metformin	Women without metformin use, including women without T2D	OS: HR 0.76 (95% CI 0.60–0.97)
Xiao et al. 2014	Hospital-based cohort	China	2002–2006	Cohort size 5,785 luminal-type breast cancers of which 680 in women with T2D, and 219 in metformin users	Non-metformin-treated women with T2D	Luminal A OS: HR 0.28 (95% CI 0.12–0.66), Luminal B (high Ki-67) OS HR 0.31 (95% CI 0.18–0.54), Luminal B (HER2 +) OS: HR 0.49 (95 % CI 0.25–0.98)
Calip et al. 2015	Population-based cohort	USA	1990–2008	Cohort size 4,216 of which 610 women with T2D and 106 in women who used metformin prior to cancer diagnosis	Non-metformin-treated women with T2D	OS: HR 0.59 (95% CI 0.40–0.85), BCSM: HR 0.67 (95% CI 0.35–1.27)
Kim et al. 2015	Register-based cohort	Korea	1997–2007	Cohort size 7,353 of which 386 breast cancers in women with T2D and 202 in metformin users	Non-metformin-treated women with T2D	DFS: HR 0.63 (95 % CI 0.42–0.94), OS: HR 0.53 (95 % CI 0.36–0.80)

Study	Design	Country	Period	Patients	Reference group	Main results
Vissers et al. 2015	Register-based cohort	UK	1998–2012	1,763 breast-cancer patients with T2D of which 1,125 metformin users	Non-metformin-treated women with T2D	In women with prevalent T2D: BCSM: HR 0.78 (95% CI 0.55–1.12), OS: HR 0.85 (95% CI 0.67–1.07), metformin use over 2 years BCSM: HR 0.47 (95% CI 0.26–0.82)

OS = overall survival, BCSM = breast-cancer-specific mortality, DSM = disease-specific mortality, DFS = disease-free survival, T2D = type 2 diabetes, DM = diabetes mellitus, HR = hazard ratio, CI = confidence interval

2.3.4 Statins and breast cancer

Proliferating cells, including cancer cells, need lipids for membrane construction, energy homeostasis and lipid-signalling functions (Antalis, Uchida, Buhman, & Siddiqui, 2011; Cedo, Reddy, Mato, Blanco-Vaca, & Escola-Gil, 2019). In addition, as breast cancer is in most cases oestrogen-dependent, steroid synthesis from cholesterol is an important factor in breast-cancer development (Antalis et al., 2011; Nelson et al., 2013). Although a direct unfavourable association between LDLs and breast cancer has been seen in *in vivo* studies (Cedo et al., 2019), epidemiological studies on the association between statins and breast cancer have reported variable results.

The majority of studies on breast-cancer risk in statin users have not found an association between statin use and breast-cancer incidence (Beck, Wysowski, Downey, & Butler-Jones, 2003; Borgquist et al., 2016; Boudreau et al., 2004; Boudreau et al., 2007; T. F. Chan, Wu, Lin, & Yang, 2014; Coogan et al., 2002; Desai et al., 2013; Dumasia, Lobocki, Couturier, Lebeis, & Drelichman, 2006; Eliassen, Colditz, Rosner, Willett, & Hankinson, 2005; Pocobelli et al., 2008; Setoguchi, Glynn, Avorn, Mogun, & Schneeweiss, 2007; Woditschka, Habel, Udaltsova, Friedman, & Sieh, 2010). However, McDougall et al. (2013) reported an increased risk, at least in long-term statin users. A decreased incidence of breast cancer has also been reported (Kochhar, Khurana, Bejjanki, Caldito, & Fort, 2005) and in other studies this has been the case at least with lovastatin use (Murakami et al., 2016) and use of some other lipophilic statins (Cauley et al., 2006) (Table 9).

Statin use has been linked to better survival in meta-analyses concerning the prognosis of breast-cancer patients (Mansourian et al., 2016; Wu et al., 2015). However, in some meta-analyses, this favourable association has been seen only in connection with lipophilic statins (B. Liu, Yi, Guan, Zeng, & Ma, 2017; Manthravadi, Shrestha, & Madhusudhana, 2016).

Most of the original studies on statin use and survival of breast cancer patients have not observed an association between statin use and breast-cancer-specific mortality or overall survival (Brewer et al., 2013; Desai et al., 2015; Nickels et al., 2013; Smith et al., 2016). On the other hand, some previous studies have reported better prognosis in terms of breast-cancer-specific mortality and overall survival in statin users compared with non-users (Borgquist, Broberg, Tojjar, & Olsson, 2019; Murtola, Visvanathan, Artama, Vainio, & Pukkala, 2014). A study by Cardwell et

al. (2015) observed lower overall survival in breast-cancer patients with post-diagnostic statin use (Table 10).

There are only two studies in which the association between statin use and survival of breast-cancer patients has been explored in women with diabetes (Borgquist et al., 2019; Ceacareanu et al., 2011). In these studies, favourable outcomes as regards overall survival (Ceacareanu et al., 2011) and breast-cancer-specific mortality (Borgquist et al., 2019) were reported in statin users.

Table 9. Studies on breast cancer incidence in relation to statin use.

Study	Design	Country	Period	Patients	Breast cancer incidence
Coogan et al. 2002	Hospital-based case-control	USA	1987–2001	906 breast cancers of which 78 in statin users	OR* 1.2 (95% CI 0.70–2.00)
Beck et al. 2003	Register-based cohort	Canada	1989–1997	Cohort size 67,472; 879 breast cancers of which 188 in statin users	HR 1.09 (95% CI 0.93–1.28)
Boudreau et al. 2004	Population-based case-control	USA	1997–1999	975 breast cancers of which 112 in statin users	OR* 0.9 (95% CI 0.70–1.20)
Eliassen et al. 2005	Cohort (Nurses' Health Study)	USA	1988–2000	Cohort size 75,828; 3,177 breast cancers of which 237 in statin users	HR 0.99 (95% CI 0.86–1.13)
Kochhar et al. 2005	Register-based cohort	USA	1998–2004	Cohort size 40,421; 556 breast cancers	OR* 0.49 (95% CI 0.38–0.60)
Cauley et al. 2006	Cohort	USA	1993–2004	Cohort size 156,351; 4,383 breast cancers of which 297 in statin users	Lipophilic statins HR 0.82 (95% CI 0.70–0.97), all statins HR 0.91 (95% CI 0.80–1.05)
Dumasia et al. 2006	Hospital-based case-control	USA	1995–2005	521 breast cancers of which 29 in statin users	Over 4 years of statin therapy OR 0.78 (95% CI 0.47–1.31)
Boudreau et al. 2007	Register-based cohort	USA	1990–2004	Cohort size 92,788; 2,707 breast cancers of which 130 in statin users	HR 1.07 (95% CI 0.88–1.29)
Pocobelli et al 2008.	Population-based case-control	USA	1995–2001	3,859 breast cancers of which 280 in statin users	Lipophilic statins OR* 1.0 (95% CI 0.80–1.20)
Eaton et al. 2009	Hospital-based case-control	USA	2005–2008	95 breast cancers of which 40 in statin users	OR* 1.3 (95% CI 0.70–2.50)
Woditschka et al. 2010	Case-control	USA	1997–2007	22,488 breast cancers of which 5,409 in lipophilic-statin users	Lipophilic-statin users OR* 1.02 (95% CI 0.97–1.08)
McDougall et al. 2013	Population-based case-control	USA	2000–2008	1,897 breast cancers of which 451 in statin users	Use of statins 10 years or longer: IDC OR* 1.83 (95% CI 1.14–2.93), ILC OR* 1.7 (95% CI 1.25–3.12)

Study	Design	Country	Period	Patients	Breast cancer incidence
Desai et al. 2013	Cohort (WHI Trial and observational study)	USA	1993–2010	Cohort size 154,587; 5,427 breast cancers of which 366 in statin users	HR 0.94 (95% CI 0.83–1.06)
Chan et al. 2014	Population-based case-control	USA	2004–2011	565 breast cancers	OR* 1.13 (95% CI 0.84–1.51)
Borgquist et al. 2016	Cohort (NHS)	USA	2000–2012	Cohort size 77,845; 3,055 breast cancers of which 1,078 in statin users	HR 1.0 (95% CI 0.92–1.2)
Murakami et al. 2016	Register-based case-control	Taiwan	2004–2010	4,332 breast cancers of which 632 in statin users	Lovastatin OR* 0.60 (95% CI 0.50–0.71), atorvastatin OR* 0.89 (95% CI 0.78–1.01)

OR = odds ratio, CI = confidence interval, RR = risk ratio, HR = hazard ratio, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, WHI = Women's Health Initiative

* Reported ORs are more likely to be HRs based on the study designs (Knol et al., 2008).

Table 10. Studies of breast cancer survival in relation to statin use.

Study	Design	Country	Period	Patients	Main results
Ceacareanu et al. 2011	Hospital-based cohort	USA	2003–2007	225 breast cancer patients with diabetes	OS: HR 0.23 (95% CI 0.08–0.66) DFS: HR 0.27 (95% CI 0.10–0.71)
Brewer et al. 2013	Hospital-based cohort	USA	1995–2011	723 inflammatory breast cancer patients, of which 73 statin users	PFS: HR 0.63 (95% CI 0.42–0.96) OS: HR 1.00 (95% CI 0.63–1.60) DSM: HR 0.95 (95% CI 0.58–1.56)
Nickels et al. 2013	Population-based cohort	Germany	2001–2005	3,189 breast cancer patients of which 305 statin users	OS: HR 1.21 (95% CI 0.87–1.69) BCSM: HR 1.04 (95% CI 0.67–1.60)
Murtola et al. 2014	Population-based cohort	Finland	1995–2003	31,236 breast cancer patients of which 4,151 statin users	Prediagnostic statin user BCSM: HR 0.54 (95% CI 0.44–0.67), OS: 0.58 (95% CI 0.49–0.70)
Cardwell et al. 2015	Register-based cohort	UK	1998–2009	17,880 breast cancer patients of which 4,282 statin users	BCSM: HR 0.84 (95% CI 0.68–1.04) OS: HR 0.84 (95% CI 0.72–0.97)
Desai et al. 2015	Cohort	USA	–2010	7,883 breast cancer patients	BCSM: HR 0.59 (95% CI 0.32–1.06)
Smith et al. 2016	Register-based cohort	Ireland	2001–2011	4,243 breast cancer patients of which 837 statin users	BCSM: HR 0.88 (95% CI 0.66–1.17) OS: HR 1.00 (95% CI 0.82–1.21)
McMenamin et al. 2016	Register-based cohort	Scotland	2009–2012	15,140 breast cancer patients of which 3 031 statin users	Prediagnostic statin use BCSM: HR 0.85 (95% CI 0.74–0.98), OS: HR 0.75 (95% CI 0.67–0.84)
Borgquist et al. 2019	Register-based cohort	Sweden	2005–2012	20,559 breast cancer patients of which 2,742 prediagnostic statin users	BCSM: HR 0.77 (95% CI 0.63–0.95) OS: HR 0.76 (95% CI 0.66–0.88) Patients with DM BCSM: HR 0.63 (95% CI 0.40-0.99)

OS = overall survival, DFS = disease-free survival, PFS = progression-free survival, BCSM = breast-cancer-specific mortality, HR = hazard ratio

3 Aims of the present study

The aim of the study was to enrich the evidence concerning metformin and statin use and the incidence and prognosis of both ovarian and breast cancer in women with T2D.

The specific aims of this study were:

1. To find out whether or not metformin and/or statin use is associated with a lower risk of ovarian cancer in women with T2D.
2. To find out whether or not metformin and/or statin use is associated a better prognosis of ovarian cancer in women with T2D.
3. To find out whether or not antidiabetic medication and/or statin use is associated with a lower incidence of breast cancer in women with T2D.
4. To find out whether or not metformin and/or statin use is associated with a better prognosis of breast cancer in women with T2D.

4 Materials and methods

4.1 FinDM database

The 'Diabetes in Finland' database (FinDM) was originally designed to provide nationwide information on the state of care of persons with diabetes in Finland. The database enables monitoring of the incidence and prevalence of diabetes, its long-term complications and also, the costs of diabetes both nationally and regionally (Sund & Koski, 2009). Comparison of FinDM data against a regional diabetes register covering the Helsinki district has shown good agreement (Sund, Harno, Ranta, & Tolppanen, 2010).

The FinDM database combines information from different national health care registers in Finland (Figure 6). From the registers of the National Institute for Health and Welfare, FinDM has the Care Register for Health Care, the Finnish Hospital Discharge Register and the Hospital Benchmarking Database, which includes diagnoses from hospital records since 1969 for inpatients and since 1998 also for outpatients. In addition, data on gestational diabetes is available from the Birth Register maintained by the National Institute for Health and Welfare. From the registers of the Social Insurance Institution of Finland, FinDM has obtained data from the Special Refund Entitlement Register and Prescription Register, which includes details of purchases, of, among other things, antidiabetic medication and statins from 1994 enabling to track the use of these medications. The FinDM database also includes information from the Causes of Death Register, which is maintained by Statistics Finland. All this register data is used to identify the persons with diabetes in Finland, as comprehensively as possible (Sund & Koski, 2009).

4.2 The Finnish Cancer Registry

The Finnish Cancer Registry (FCR) was founded in 1952. It is based on the total population and identifies persons by means of personal identity codes (PICs). Notification of cancer is obligatory in Finland and information can be provided to the registry from multiple sources, including hospitals, primary care, pathology and cytology laboratories and death certificates. All Nordic Cancer Registries, including the FCR, hold high-quality data in terms of completeness and accuracy (Pukkala et al., 2018).

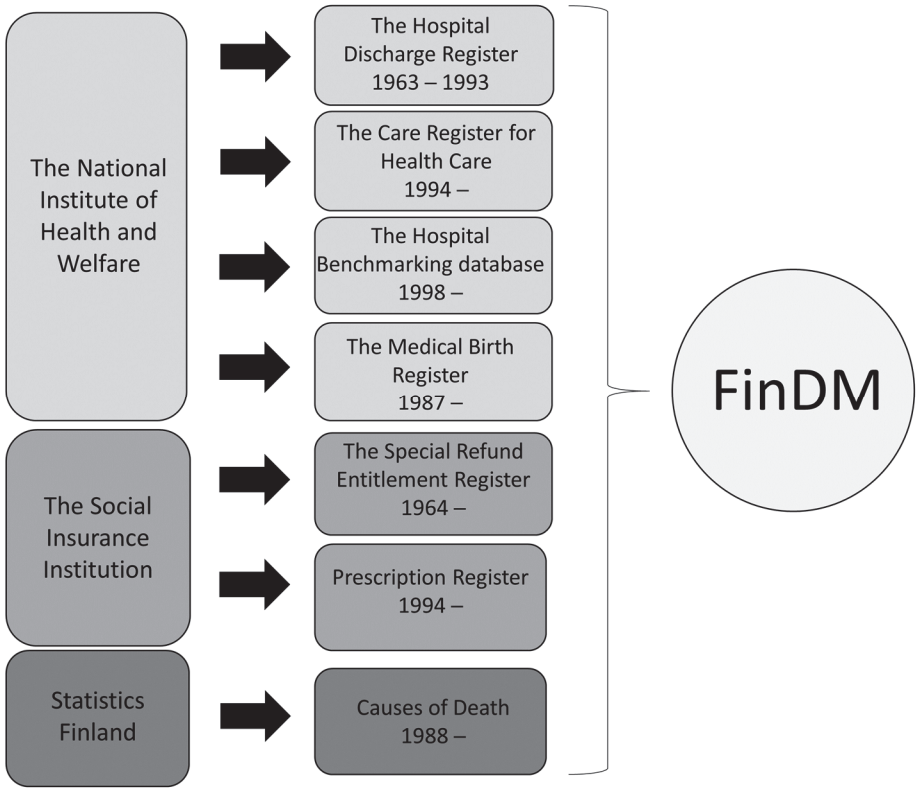

Fig. 6. Description of the 'Diabetes in Finland' database (FinDM). Figure adapted from Sund & Koski (2009).

4.3 Study population, data collection and study design

The source population for all four studies is that registered in the FinDM database.

4.3.1 Studies I and III

Studies I and III are cohort studies including nested case-control analyses. Study I is focused on ovarian cancer and Study III on breast cancer incidence. For Studies I and III, we first identified (from the FinDM database) women with newly diagnosed T2D between the 1st of January 1996 and the 31st of December 2011. The restriction to T2D cases which were newly diagnosed during this accrual

period was a result of the fact that the data on purchases of relevant medications with sufficient completeness and quality was available only for this period. PICs were used to link the information between the FinDM database and the FCR. The entry date to follow-up of the incidence of the target cancer was either the date of the 40th birthday or the date when one year had passed from the diagnosis of T2D, whichever occurred later. The age limit of 40 was set because of the rarity of ovarian- and breast-cancer cases in younger age groups and also in order to avoid possible misclassification of diabetes type in the study cohort. Starting follow-up no earlier than one year after the diagnosis of T2D, and excluding exposures in the year immediately prior to the date of diagnosis of target cancer was carried out to allow a minimum latency period for any medication effect on the hazard of cancer and to help reduce the detection bias and reverse causality bias associated with temporal closeness of cancer diagnosis with diagnosis of T2D or initiation of antidiabetic medication. Women who were diagnosed with the target cancer prior to the start of follow-up were excluded from the study. Also, women with certain previous gynaecological operations (oophorectomy, salpingo-oophorectomy or hysterectomy with bilateral salpingo-oophorectomy) were excluded from Study I. It is plausible that some women with prior operations remained in the cohort because data on surgical operations were available only from 1987, but this mainly concerned women in the older age range. The final cohort in Study I contained 137,643 eligible women with incident T2D (Figure 7) and in Study III the total was 141,194 (Figure 8).

A nested case-control analysis, in which the control subjects were selected according to the sampling design, was also performed in order to evaluate the possible association with the target cancer and the cumulative use of different forms of medication. A nested case-control analysis enables more straightforward calculation of the defined daily doses (DDDs) of medication used by each woman before their index date, when analysing the association between the accumulated DDD and target cancer incidence. For each case subject, up to 20 controls were matched for both age (date of birth ± 182 days) and duration of diabetes (± 182 days) and selected from the cohort among those members who were alive, under follow-up and without a history of the target cancer at the time of target cancer diagnosis of the case subject.

Exposure to medication was evaluated by using four indicators, the use at any time (‘ever-use’) of metformin, other forms of oral antidiabetic medication, insulins and statins. Medication use was considered to be a time-varying covariate. Exposure to these medications was considered to begin 365 days after its first

purchase in both cohort analysis and the nested case-control analysis, i.e. each individual's follow-up time was classified as unexposed to a given medication until 365 days after the first record of a purchase of the medication in question, and exposed afterwards. For example, if a woman was using metformin at the start of follow-up, throughout the entire follow-up she was considered as exposed to metformin. On the other hand, if the woman then switched to insulin later during follow-up, the exposure status in her remaining follow-up time was coded as exposed to both metformin and insulin, starting 365 days after the first purchase of insulin, and her follow-up before that point remained classified as unexposed to insulin. Such a person would thus contribute person-years to being exposed to both metformin and insulin, as well as person-years to being unexposed to insulin.

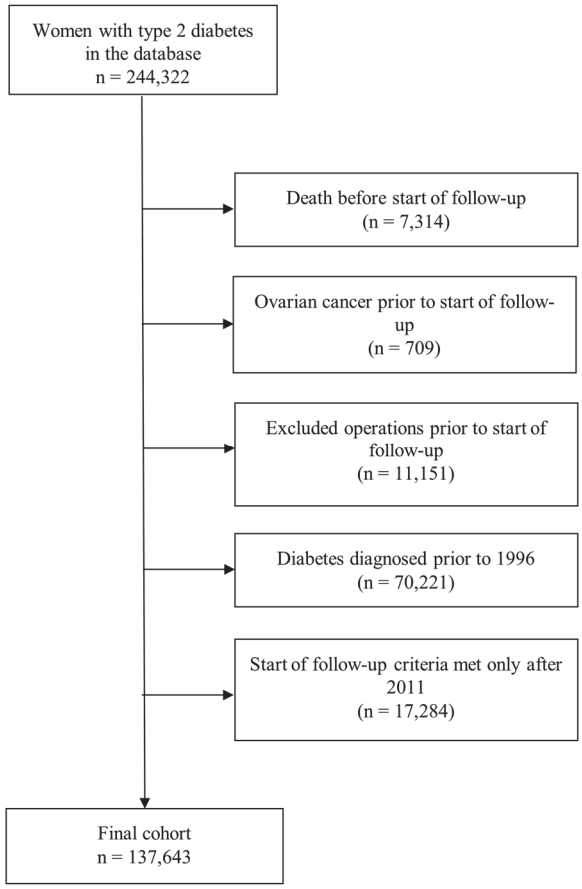

Fig. 7. Flowchart in Study I.

The association between cumulative use of these medications and target cancer incidence was assessed in the nested case-control analysis by using the total amount of purchased DDDs during the follow-up time.

Follow-up ended on the date of diagnosis of target cancer, oophorectomy for reasons other than cancer (in Study I), death, or the end of the study period (31st of December 2011).

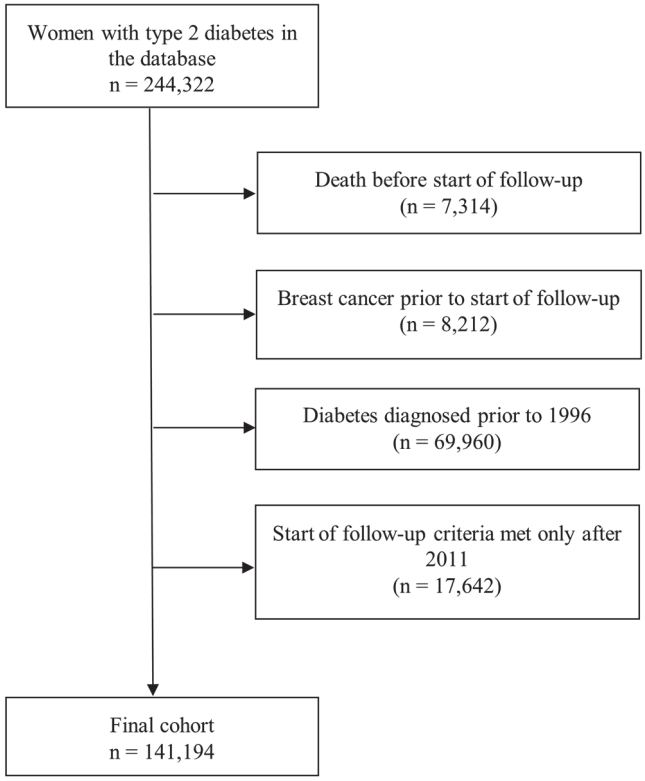

Fig. 8. Flowchart in Study III.

4.3.2 Study II

Study II is a cohort study. For this study, in the FinDM database we identified those women who were diagnosed with epithelial ovarian cancer between the 1st of January 1998 and the 31st of December 2011 (n = 757). We excluded those women who had a prior cancer diagnosis (other than non-melanoma skin cancer), whose

estimated duration of T2D was less than 180 days before ovarian cancer diagnosis, and those whose ovarian cancer was diagnosed at autopsy. Data on the cancer cases, histology and stages were obtained from the FCR by using the PICs of women in the FinDM database. Stage was categorised as local, advanced or unknown. The final study cohort consisted of 421 women with T2D who were diagnosed with epithelial ovarian cancer at least 180 days after the diagnosis of T2D in 1998─2011 (Figure 9).

Women were categorised into mutually exclusive groups according to antidiabetic medication purchased during the three years before ovarian cancer diagnosis: metformin only, other oral ADM only, metformin and other oral ADM, insulin at any time and no history of ADM. Women were also classified as statin users and non-users. For all medications, exposure was considered to begin 180 days after its first purchase to avoid reverse-causation bias. A woman was classified as a metformin or other oral ADM user if she had purchased these medications for 180 days or longer in the three-year period preceding ovarian-cancer diagnosis, with no history of insulin purchases. If she had purchased these medications for less than 180 days, she was categorised into the group 'no history of ADM use'. Only one purchase of insulin was enough to classify a woman into the group 'insulin at any time'. Similarly, a woman was categorised as a statin user if she had purchased statin for 180 days or longer in the three years preceding the diagnosis of ovarian cancer. The cumulative use of medication was estimated by DDDs purchased within the three years before ovarian cancer diagnosis.

Individual follow-up started at the date of ovarian-cancer diagnosis and ended at the time of death, emigration or the closing of follow-up (31st of December 2013), whichever happened earliest.

Follow-up data was obtained from the FCR and using PICs, the records were matched with information in the FinDM database, the Central Population Register and Causes of Death Statistics. Deaths were classified into two categories, deaths from ovarian cancer, and deaths resulting from other causes. Information on emigration was obtained from the Central Population Register.

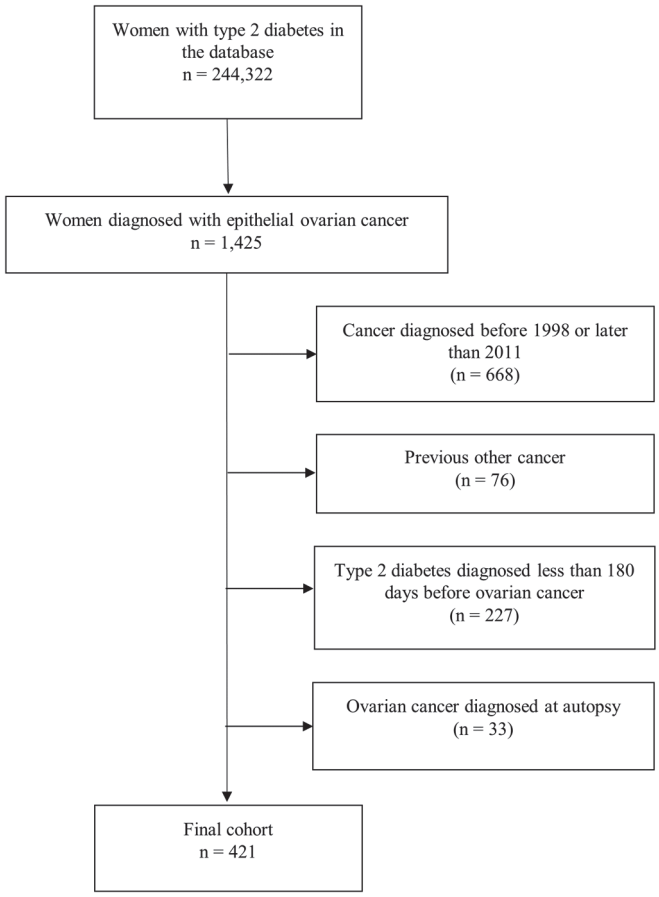

Fig. 9. Flowchart in Study II.

4.3.3 Study IV

Study IV is a cohort study. Women who were diagnosed with breast cancer between the 1st of January 1998 and the 31st of December 2011 were identified in the FinDM database. Women who were at least 40 years old when T2D was diagnosed and in whom the estimated duration of T2D was at least 180 days during the three years before breast-cancer diagnosis were included in the study. We excluded those women who had a prior cancer diagnosis (other than non-melanoma skin cancer) and those whose breast cancer was diagnosed only at autopsy. Data on the cancer

cases, histology and stages were obtained from the FCR by using PICs of women in the FinDM database. Stage was categorised roughly as local, advanced or unknown. The final study cohort consisted of 3,533 women with T2D who were diagnosed with breast cancer at least 180 days after the diagnosis of T2D in 1998─2011 (Figure 10).

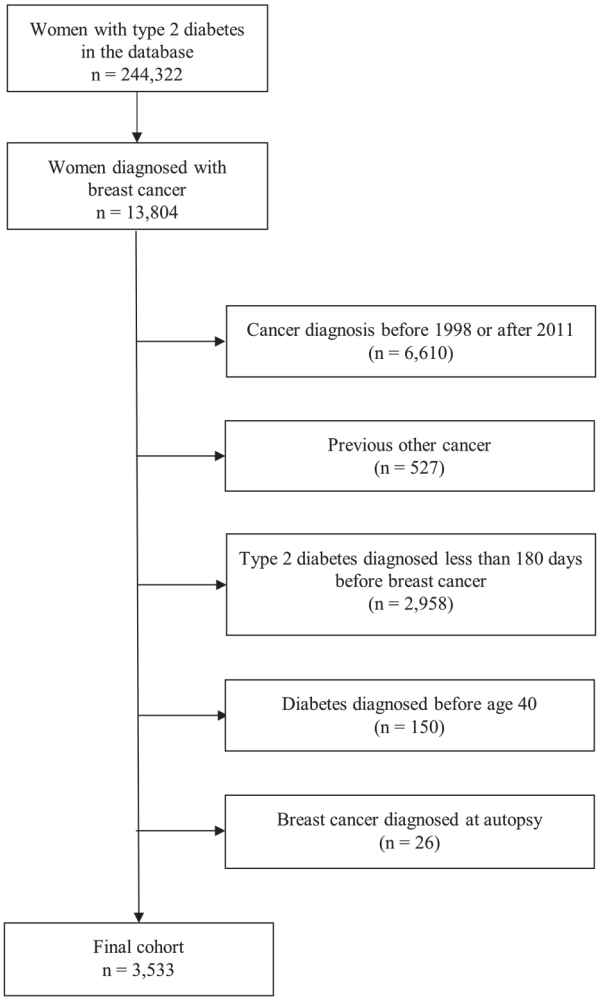

Fig. 10. Flowchart in Study IV.

Women were categorised into mutually exclusive groups according to antidiabetic medication purchased during the three years before breast-cancer diagnosis: metformin only, other oral ADM only, metformin and other oral ADM, insulin at any time and no history of ADM. In addition, women were classified as statin users and non-users. For all medications, exposure was esteemed to begin 180 days after its first purchase. A woman was classified as a metformin or other oral ADM user if she had purchased these medications for 180 days or longer in the three-year period preceding breast-cancer diagnosis, with no history of insulin purchases. Correspondingly, if she had purchased these medications for less than 180 days, she was categorised into the group 'no history of ADM use'. Even one purchase of insulin was enough to classify a woman into the group 'insulin at any time'. Similarly, a woman was categorised as a statin user if she had purchased statin for 180 days or longer in the three years preceding the diagnosis of breast cancer. The cumulative use of different medications was estimated by DDDs purchased within the three years before breast-cancer diagnosis.

Individual follow-up began at the date of breast-cancer diagnosis and ended at the time of death, emigration or the closing of follow-up (31st of December 2013), whichever happened earliest.

Follow-up data was obtained from the FCR, and using PICs, the records were matched with information in the FinDM database, the Central Population Register and Causes of Death Statistics. Deaths were classified into two categories, deaths from breast cancer, and deaths resulting from other causes. Information on emigration was obtained from the Central Population Register.

4.4 Statistical methods

4.4.1 Studies I and III

In both Studies I and III, in the full-cohort analysis a Poisson regression model (Loomis, Richardson, & Elliott, 2005) was used to estimate hazard ratios (HRs) with 95% confidence intervals (95% CIs) of the incidence of the target cancer (ovarian cancer in Study I and breast cancer in Study III) in relation to ever-use of metformin, other types of oral antidiabetic medication, insulins and statins. Also, the effects of current age and duration of T2D were assumed to obey piecewise constant hazards patterns over chosen intervals. Age was split into 5-year intervals from 40 to 89 years plus one more interval covering women over 90 years old.

Duration of diabetes was split into intervals of one to three years, three to five years, five to eight years and eight to 16 years.

In the nested case-control analyses, in both Studies I and III conditional logistic regression analysis (Keogh & Cox, 2014) was utilised to estimate HRs with 95% CIs in relation to the use of metformin, other types of oral antidiabetic medication, insulins and statins. Cumulative doses were classified according to tertiles of the total amounts of DDDs used.

The register data were pre-processed using SAS/STAT® software version 9.4 of the SAS System for Windows. Consecutive data transformations and the statistical analyses were performed in R environment version 3.3.2 (R Core Team, 2017).

4.4.2 Studies II and IV

Mortality from the target cancer (ovarian or breast) and from other causes was described in different medication groups (metformin only, other oral ADM only, metformin and other oral ADM, insulin at any time and no history of ADM) by using the Aalen─Johansen estimator of the cumulative incidence function for competing risks (deGlas et al., 2016; Putter, Fiocco, & Geskus, 2007). Cox proportional hazards models were fitted for the two causes of death: target cancer or other causes separately, adjusting for the effects of calendar year, age, duration of T2D and stage at the diagnosis of target cancer. HRs with 95% CIs for the two causes of death in relation to different medication groups were estimated from the adjusted Cox models. An interaction term was included in the models to evaluate the possible joint effect of ADM and statin use. Supplementary analyses were also performed in which the medication group membership indicators in the Cox models were replaced with cubic spline terms for the total amount of DDDs of each type of purchased medication (Heinzl & Kaider, 1997).

R environment version 3.3.2 (in Study II) and version 3.5.1 (in Study IV) were used throughout for both data preparation and statistical analysis. The Cox models were fitted, and assumptions checked with functions provided in the ‘survival’ package (R Core Team, 2017; Therneau, 2015).

4.5 Ethical aspects

For all four studies, no separate ethic approval or informed consent was needed according to Finnish legislation because we utilised only administrative registers.

However, ethic approval was obtained for the FinDM study from the research ethics committee of the National Institute of Health and Welfare (30th of January 2014, meeting 1/2014, § 609). Permission to use data was obtained from the maintainers of the original registers (National Institute of Health and Welfare, Social Insurance Institution and Statistics Finland). Data received by the research group were anonymized such that the PICs were converted into unified codes. The data of each individual were handled according to Finnish data-protection legislation.

5 Results

5.1 The association between metformin and statin use and ovarian cancer incidence in women with T2D (Study I)

The final cohort comprised 137,643 women with T2D. During the follow-up period, from 1996─2011, 303 were diagnosed with epithelial ovarian cancer. The incidence of ovarian cancer was age-dependent, being highest between the ages of 60 to 69 years (51.4 per 100,000 person-years). The incidence of ovarian cancer was highest in those women who had had T2D for 5─8 years (52.5 per 100,000 person-years) (Table 11).

In the full-cohort analysis, ever-use of metformin was not found to be associated with ovarian-cancer incidence when compared with ever-use of other types of oral antidiabetic medication. The adjusted hazard ratio (HR) was 1.02 (95% confidence interval [CI] 0.72─1.45) for metformin users and 1.19 (95% CI 0.73─1.93) for insulin users when compared with users of other types of oral ADM. The incidence of ovarian cancer was not found to be associated with statin use, having an HR of 0.99 (95% CI 0.78─1.25) compared with no use of statins.

In the case-control analysis, the results remained similar; ever-use of metformin had an adjusted HR of 0.91 (95% CI 0.61─1.34) and ever-use of insulin had an adjusted HR of 1.19 (95% CI 0.72─1.97) when compared with use of other forms of oral antidiabetic medication. The use of statins was not found to be associated with the incidence of ovarian cancer (HR 0.96 [95% CI 0.75─1.23]). We saw no interaction between metformin and statin use as regards the incidence of ovarian cancer. Rising cumulative use of ADM or statins was not observed to have an association with ovarian-cancer incidence.

5.2 Ovarian cancer prognosis in women with T2D using antidiabetic medication or statins (Study II)

The final study cohort consisted of 421 patients diagnosed with epithelial ovarian cancer. The majority of ovarian cancer diagnoses were made among women of 70 to 79 years old (38%). In most cases, ovarian cancer was at an advanced stage at the time of diagnosis (78%) (Table 12). The median follow-up time was 2.2 years.

Many women used metformin combined with other types of oral ADM (24%), while 18% used metformin as the only ADM, 14% used only other types of oral

ADM, 19% used insulin and 25% of women did not have a history of any ADM use. Women who used only metformin, tended to be younger (median 69 years old) and the duration of diabetes was shorter (3.1 years) (Table 12).

Table 11. Incidence of ovarian cancer (per 100,000 person-years), distribution of person-years at risk, and numbers (%) of cases and their matched controls according to age, duration of diabetes and medication use (Study I).

Variable	Incidence (per 100,000 person-years)	Person-years in cohort	Cases (%)	Controls (%)
Age (years)				
40–49	12.7	47,229	6 (2.0)	126 (2.1)
50–59	28.9	127,996	37 (12.2)	739 (12.0)
60–69	51.4	194,406	100 (33.9)	2,000 (33.0)
70–79	49.5	216,225	107 (35.3)	2,140 (35.3)
80–89	35.9	142,166	51 (16.8)	1,023 (16.9)
90–106	9.9	20,260	2 (0.7)	41 (.07)
Duration of diabetes (years)				
1–3	38.0	239,473	91 (30.0)	1,903 (31.4)
3–5	38.1	175,744	67 (22.1)	1,289 (21.3)
5–8	52.5	177,254	93 (30.7)	1,771 (29.2)
Metformin use				
Ever	41.1	486,197	200 (66.0)	4,080 (67.3)
Never	39.3	262,085	103 (34.0)	1,980 (32.7)
Other oral antidiabetic medication use				
Ever	40.8	367,964	150 (49.5)	2,978 (49.1)
Never	40.2	380,319	153 (50.5)	3,082 (50.9)
Insulin use				
Ever	43.4	87,654	38 (12.5)	658 (10.9)
Never	40.1	660,629	265 (87.5)	5,402 (89.1)
No antidiabetic medication	33.9	141,745	48 (15.8)	1081 (17.8)
Statin use				
Ever	42.8	371,806	159 (52.5)	3,235 (53.4)
Never	38.2	376,476	144 (47.5)	2,825 (46.6)

There were 186 women (44%) who used statins. Statin users and non-users were similar as regards age distribution, duration of diabetes and ovarian cancer stage at the time of diagnosis (Table 12). In the majority of the patients, lipophilic statins were used, i.e. simvastatin was used in 56% and atorvastatin in 27% of women.

In total, 310 (74%) patients died during the follow-up period, mostly due to the ovarian cancer itself (276 patients, 89%) (Table 13). Unadjusted cumulative mortality from ovarian cancer by 10 years after diagnosis varied from 61 to 80% across the different ADM groups and from 69 to 73% between the groups defined by statin use (Figure 11). On the other hand, mortality from other causes by 10 years was 10% on average, with less variability across different medication groups.

Mortality rates in connection with ovarian cancer and other causes were not found to differ according to ADM use when adjusted for age, stage, use of statins, calendar year and duration of diabetes at diagnosis of ovarian cancer. Metformin as the only ADM had an adjusted HR of 1.15 (95% CI 0.74─1.79) for ovarian cancer death and an adjusted HR of 1.85 (95% CI 0.44─7.73) for death from other causes compared with the use of other types of oral ADM. However, prediagnostic use of statins was found to be associated with decreased mortality from ovarian cancer (adjusted HR 0.72, 95% CI 0.56─0.93) but not mortality from other causes (adjusted HR 0.66, 95% CI 0.30─1.43) compared with no use of statins (Table 13).

No association was seen between cumulative use of metformin or statins (DDDs) and mortality from ovarian cancer.

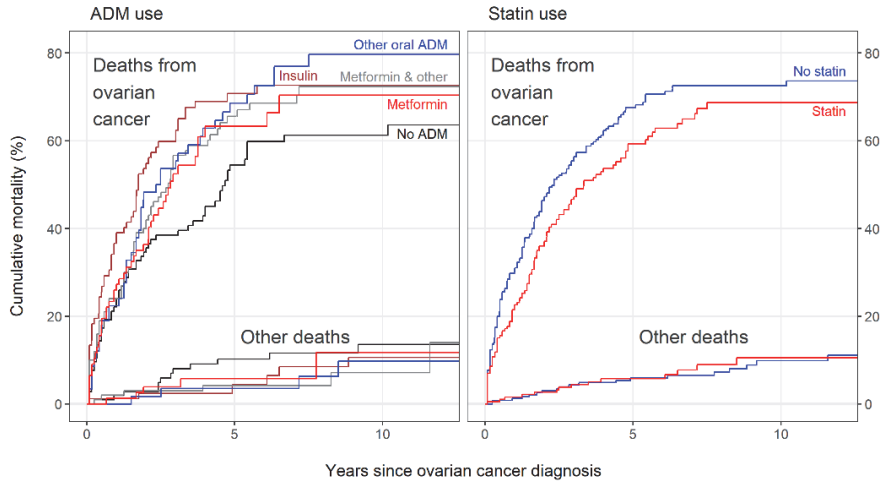

Fig. 11. Cumulative mortality curves of death from ovarian cancer and from other causes in different medication groups (Study II).

Table 12. Distribution of baseline characteristics in different medication groups (Study II).

Variable	Antidiabetic medication					Statin use		
	Metformin	Other oral ADM	Metformin and other oral ADM	Insulin	No use of ADM	Yes	No	Total
Number of patients	77	58	100	82	104	186	235	421
Age at diagnosis, years								
Median	69	75	70	71	72	71	71	71
IQR	63–77	66–80	61–77	65–78	64–79	65–77	62–78	64–78
Age categories, years (%)								
42–59	8 (10)	6 (10)	19 (19)	9 (11)	17 (16)	18 (10)	41 (17)	59 (14)
60–69	33 (43)	13 (22)	31 (31)	28 (34)	27 (26)	66 (35)	66 (28)	132 (31)
70–79	30 (39)	24 (41)	42 (42)	29 (35)	35 (34)	74 (40)	86 (37)	160 (38)
80–92	6 (8)	15 (26)	8 (8)	16 (20)	25 (24)	28 (15)	42 (18)	70 (17)
Duration of T2D, years (%)								
Median	3.1	5.0	6.2	10.8	7.0	6.3	5.7	6.2
IQR	2.0–5.5	3.1–8.3	4.1–8.9	6.8–15.0	2.0–10.1	3.1–10.0	3.1–10.0	3.1–10.1
0.5 – < 3	37 (48)	15 (26)	13 (13)	4 (5)	34 (33)	45 (24)	58 (25)	103 (24)
3 – < 6	24 (31)	20 (34)	30 (30)	13 (16)	13 (12)	40 (22)	60 (26)	100 (24)
6 – < 12	14 (18)	19 (33)	44 (44)	30 (37)	41 (39)	71 (38)	77 (33)	148 (35)
12 – < 34	2 (3)	4 (7)	13 (13)	35 (43)	16 (15)	30 (16)	40 (17)	70 (17)
Stage (%)								
Local	14 (18)	6 (10)	11 (11)	11 (13)	10 (10)	24 (13)	28 (12)	52 (12)
Advanced	58 (75)	45 (78)	77 (77)	64 (78)	86 (83)	142 (76)	188 (80)	330 (78)
Unknown	5 (6)	7 (12)	12 (12)	7 (9)	8 (8)	20 (11)	19 (8)	39 (9)

IQR = Interquartile range, ADM = antidiabetic medication

Table 13. Results from the Cox proportional hazard models for mortality from ovarian cancer and from other causes, with adjusted hazard ratios (HRs) (Study II).

		Mortality from ovarian cancer			Mortality from other causes		
Variable	Group size	Deaths	HR	(95% CI)	Deaths	HR	(95% CI)
Year of diagnosis							
1998–2002	115	84	1.00	Ref.	13	1.00	Ref.
2003–2007	149	106	1.17	(0.86-1.59)	12	1.16	(0.45-2.99)
2008–2011	157	86	0.97	(0.69-1.37)	9	1.13	(0.39-3.27)
Age at diagnosis (years)							
42–59	59	30	0.67	(0.44-1.04)	1	0.18	(0.02-1.53)
60–69	132	76	1.00	Ref.	9	1.00	Ref.
70–79	160	120	1.53	(1.14-2.05)	14	2.49	(1.03-6.05)
80–92	70	50	2.88	(1.98-4.20)	10	5.40	(1.99-14.65)
Duration of diabetes (years)							
0.5–<3	103	61	1.00	Ref.	11	1.00	Ref.
3–<6	100	70	1.31	(0.91-1.90)	3	0.35	(0.09-1.36)
6–<12	148	101	1.15	(0.81-1.63)	11	0.88	(0.34-2.27)
12–<34	70	44	0.98	(0.61-1.57)	9	1.20	(0.42-3.44)
Stage							
Local	52	9	1.00	Ref.	9	1.00	Ref.
Advanced	330	256	9.05	(4.60-17.82)	19	0.80	(0.32-2.01)
Unknown	39	11	1.60	(0.66-3.89)	6	1.01	(0.32-3.23)
Prediagnostic statin use							
No	235	162	1.00	Ref.	20	1.00	Ref.
Yes	186	114	0.72	(0.56-0.93)	14	0.66	(0.30-1.43)
Prediagnostic ADM group							
Metformin	77	46	1.15	(0.74-1.79)	5	1.85	(0.44-7.73)
Other oral ADM	58	44	1.00	Ref.	4	1.00	Ref.
Metformin and other oral ADM	100	67	1.21	(0.82-1.80)	6	1.19	(0.32-4.38)
Insulin	82	59	1.49	(0.96-2.30)	7	1.61	(0.42-6.18)
None	104	60	0.69	(0.46-1.03)	12	1.48	(0.46-4.78)

HR = hazard ratio, CI = confidence interval, ADM = antidiabetic medication

5.3 The association between antidiabetic medication and statin use and breast cancer incidence in women with T2D (Study III)

In total, 2,300 women with T2D were diagnosed with breast cancer during the study period. The incidence of breast cancer was age-dependent, and, similarly to ovarian cancer, highest in the age group 60—69 (348 per 100,000 person-years). As regards the duration of T2D the incidence of breast cancer was highest in women who had suffered the condition for over eight years (314.8 per 100,000 person-years) (Table 14).

In the full-cohort analysis, metformin ever-use was not found to be associated with breast cancer incidence compared with never-use of metformin, the adjusted HR being 1.02 (95% CI 0.93–1.11). Users of insulin, however, seemed to have association with slightly increased incidence of breast cancer (HR 1.18, 95% CI 1.03–1.35) compared with insulin never-users. The incidence of breast cancer was not related to statin use, the HR being 0.97 (95% CI 0.89–1.95).

In the case-control analysis, the results remained similar; ever-users of metformin had an adjusted HR of 0.94 (95 % CI 0.86–1.04) and insulin ever-users an adjusted HR of 1.18 (95% CI 1.03–1.36) when compared with never-users of these medications. The use of statins was not observed to be associated with the incidence of breast cancer (HR 0.93 [95% CI 0.85–1.02)]). We observed no interaction between metformin and statin use in connection with the incidence of breast cancer.

Rising cumulative use of insulin seemed have an association with an increased breast cancer risk, the estimated HR being 1.46 (95% CI 1.19–1.81) for the amount of DDDs being 1200 or more compared with never-use of insulin (Figure 12). No consistent evidence of cumulative use of metformin, other types of oral ADM or statins was found in connection with breast cancer incidence.

Table 14. Incidence of breast cancer (per 100,000 person-years), distribution of person-years at risk, numbers (%) of cases and their matched controls according to age, duration of diabetes and medication use (Study III).

Variable	Incidence (per 100,000 person-years)	Person-years in cohort	Cases (%)	Controls (%)
Age (years)				
40–49	122	48,365	59 (2.6)	1,231 (2.7)
50–59	256.9	134,663	346 (15.0)	6,903 (15.1)
60–69	348.1	205,392	715 (31.1)	14,229 (31.1)
70–79	305.9	219,352	671 (29.2)	13,496 (29.5)
80–89	317.4	141,150	448 (19.5)	8,828 (19.3)
90–106	309	19,739	61 (2.7)	1,068 (2.3)
Duration of diabetes (years)				
1 – < 3	291.5	245,962	717 (31.2)	14,252 (31.1)
3 – <5	289.1	180,562	522 (22.7)	10,290 (22.5)
5 – < 8	306	182,027	557 (24.2)	11,238 (24.6)
8 – < 16	314.8	160,082	504 (21.9)	9,975 (21.8)
Metformin use				
Ever	301.5	502,076	1,514 (65.8)	30,588 (66.9)
Never	294.9	266,557	786 (34.2)	15,167 (33.1)
Other oral ADM use				
Ever	301.9	376,233	1,136 (49.4)	22,595 (49.4)
Never	296.6	392,400	1,164 (50.6)	23,160 (50.6)
Insulin use				
Ever	337.2	90,162	304 (13.2)	5,399 (11.8)
Never	294.2	678,471	1,996 (86.8)	40,356 (88.2)
No ADM	282.9	145,612	412 (17.9)	8,103 (17.7)
Statin use				
Ever	302.8	384,679	1,165 (50.7)	23,935 (52.3)
Never	295.6	383,954	1,135 (49.3)	21,820 (47.7)
Total	299.2	768,633	2,300 (100)	45,755 (100)

ADM = antidiabetic medication

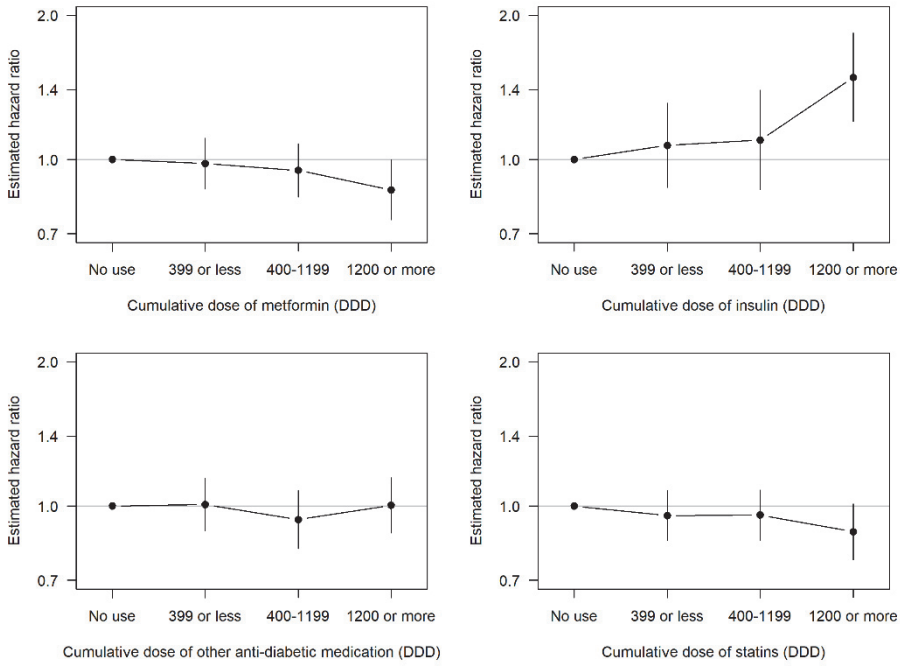

Fig. 12. Estimated hazard ratios of breast cancer by defined daily doses of different ADMs and statins, adjusted for age, duration of diabetes and use of other medications (Study III).

5.4 Breast cancer prognosis in women with T2D using antidiabetic medication or statins (Study IV)

The final study cohort consisted of 3,533 patients diagnosed with breast cancer. Most commonly, breast cancer diagnoses were among women aged 70 to 79 years (32%). In many cases, breast cancer was at local stage at the time of diagnosis (49%) (Table 15). The median follow-up period was 4.6 years.

Among ADM users, most commonly women used metformin combined with other types of oral ADM (21%), while 19% used metformin as the only ADM, 13% used only other types of oral ADM, 19% used insulin and 28% of the women did not have history of any ADM use. Women who used only metformin, were younger (median 68 years old) and the duration of T2D was shorter (3.4 years), while women in the insulin group had the longest duration of T2D (11.9 years) (Table 15).

Table 15. Distribution of baseline characteristics and outcome status in different medication groups (Study IV).

Variable	Antidiabetic medication					Statin use		
	Metformin	Other oral ADM	Metformin and other oral ADM	Insulin	No use of ADM	Yes	No	Total
Number of patients	658	444	752	686	993	1,402	2,131	3,533
Age at diagnosis, years								
Median	68	77	73	74	70	71	74	72
IQR	62–77	68–83	64–80	66–80	62–79	64–78	64–81	64–80
Age categories, years (%)								
40–59	113 (17)	43 (10)	106 (14)	74 (11)	187 (19)	166 (12)	357 (17)	523 (15)
60–69	251 (38)	95 (21)	189 (25)	185 (27)	319 (32)	499 (36)	540 (25)	1,039 (29)
70–79	209 (32)	141 (32)	254 (34)	249 (36)	275 (28)	486 (35)	642 (30)	1,128 (32)
80–100	85 (13)	165 (37)	203 (27)	178 (26)	212 (21)	251 (18)	592 (28)	843 (24)
Duration of T2D, years (%)								
Median	3.4	4.9	7.3	11.9	6.5	7.1	6.1	6.5
IQR	2.0–5.6	2.7–7.7	4.4–11.2	7.9–16.0	2.0–10.9	3.5–12.0	2.9–10.6	3.1–11.2
0.5–<3	296 (45)	128 (29)	96 (13)	30 (4)	300 (30)	300 (21)	550 (26)	850 (24)
3–<6	211 (32)	159 (36)	199 (26)	60 (9)	169 (17)	296 (21)	502 (24)	798 (23)
6–<12	118 (18)	113 (25)	302 (40)	254 (37)	327 (33)	456 (33)	658 (31)	1,114 (32)
12–<42	33 (5)	44 (10)	155 (21)	342 (50)	197 (20)	350 (25)	421 (20)	771 (22)
Stage								
Local	331 (50)	233 (52)	348 (46)	291 (42)	541 (54)	695 (50)	1,049 (49)	1,744 (49)
Advanced	291 (44)	174 (39)	355 (47)	322 (47)	387 (39)	615 (44)	914 (43)	1,529 (43)
Unknown	36 (5)	37 (8)	49 (7)	73 (11)	65 (7)	92 (7)	168 (8)	260 (7)

Variable	Antidiabetic medication					Statin use		
	Metformin	Other oral ADM	Metformin and other oral ADM	Insulin	No use of ADM	Yes	No	Total
Outcome at the end of follow-up								
Breast cancer death	88	91	119	142	160	186	414	600
Other death	75	174	221	242	221	248	685	933
Alive	495	179	412	302	612	968	1,032	2,000

IQR = interquartile range, ADM = antidiabetic medication

Statins were used by 40% of the women. Statin users and non-users were similar as regards age distribution, duration of diabetes and breast cancer stage at the time of diagnosis. The most commonly used statins were lipophilic statins, i.e. simvastatin (79%) and atorvastatin (43%).

In total, 1,533 (43%) patients died during the follow-up period; 600 from breast cancer and 933 from other causes (Table 15). The unadjusted 10-year cumulative mortality in connection with other causes varied from 22% to 46% across the different ADM groups and from 30% to 37% between the groups defined by statin use (Figure 13). Mortality from other causes was lower overall in the metformin group compared with all the other groups. Mortality from both breast cancer and from other causes was lower in the statin group than among non-users of statins.

Prediagnostic use of ADM, i.e. ADM use before breast cancer diagnosis, was not found to be associated with mortality from breast cancer. The estimated HR for metformin users was 0.86 (95% CI 0.63–1.17) compared with users of other types of oral ADM. On the other hand, prediagnostic metformin use was observed to be associated with lower mortality from other causes (HR 0.73, 95% CI 0.55–0.97) and insulin use was found to be associated with higher mortality from other causes (HR 1.45, 95% CI 1.16–1.80) compared with users of other types of oral ADM (Table 16).

Prediagnostic statin use was observed to be associated with decreased mortality from both other causes (HR 0.75, 95% CI 0.64–0.87) and breast cancer (HR 0.76, 95% CI 0.63–0.92) compared with no use of statins. However, no sufficient evidence was found for cumulative use of either metformin or statins to be associated with mortality from breast cancer. No evidence for any interaction of ADM and statin could be discerned.

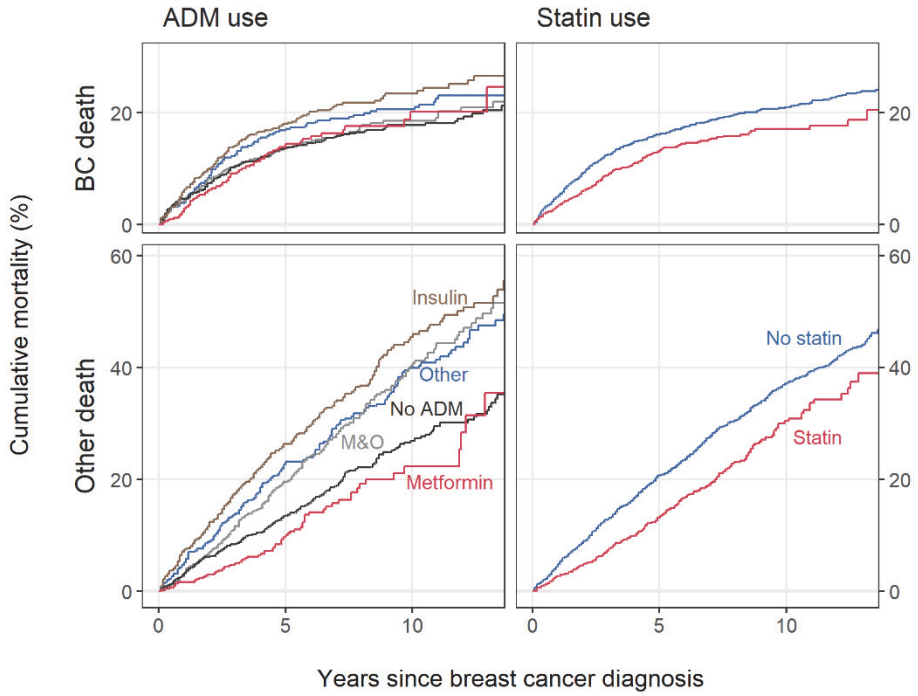

Fig. 13. Cumulative mortality curves for the two causes of death in the different medication groups. BC = breast cancer, ADM = antidiabetic medication, M&O = metformin and other oral ADM

Table 16. Results from Cox proportional hazard models of mortality from breast cancer and from other causes (Study IV).

Variable	Mortality from breast cancer Hazard ratio (95% CI)	Mortality from other causes Hazard ratio (95% CI)
Year of diagnosis		
1998–2002	Ref.	Ref.
2003–2007	0.90 (0.74–1.11)	0.93 (0.80–1.09)
2008–2011	0.98 (0.78–1.24)	0.85 (0.68–1.05)
Age at diagnosis, years		
40–59	0.94 (0.70–1.27)	0.57 (0.40–0.82)
60–69	Ref.	Ref.
70–79	1.62 (1.30–2.01)	3.03 (2.45–3.74)
80–100	2.56 (2.02–3.25)	8.17 (6.60–10.12)
Duration of diabetes, years		
0.49–<3	Ref.	Ref.
3–<6	0.94 (0.74–1.20)	0.99 (0.80–1.23)
6–<12	1.01 (0.80–1.28)	1.20 (0.98–1.46)
12–<42	1.03 (0.79–1.35)	1.21 (0.96–1.51)
Stage		
Local	Ref.	Ref.
Advanced	5.26 (4.28–6.46)	1.10 (0.95–1.26)
Unknown	2.35 (1.62–3.41)	1.49 (1.20–1.85)
Prediagnostic statin use		
No	Ref.	Ref.
Yes	0.76 (0.63–0.92)	0.75 (0.64–0.87)
Prediagnostic ADM group		
Metformin	0.86 (0.63–1.17)	0.73 (0.55–0.97)
Other	Ref.	Ref.
Metformin and other	0.80 (0.60–1.06)	1.01 (0.82–1.24)
Insulin	1.16 (0.86–1.55)	1.45 (1.16–1.80)
None	0.93 (0.71–1.21)	0.81 (0.66–0.99)

CI = confidence interval, ADM = antidiabetic medication

6 Discussion

6.1 Data quality

The major strength of our epidemiological studies is the availability of reliable and comprehensive national registers. Data quality is generally considered to be high in Finnish national registers, such as the Hospital Discharge Register (Sund, 2012). The FCR is known to be of high quality in terms of completeness, as 93% of cancer cases have been microscopically verified (Pukkala et al., 2018). Data concerning the duration of diabetes is accurate because patients' details are entered into the FinDM database at the time of the first purchase of any form of ADM or recording of diabetes diagnosis in any of the used registers. Some minor errors concerning diet-controlled diabetes can still be found in the register. Each resident of Finland is covered by public health insurance which is managed by the Social Insurance Institution (Martikainen & Rajaniemi, 2002). The Prescription Register contains details of all purchases of medications which are directly reimbursed by the Social Insurance Institute upon purchase at the pharmacy (Finnish Medicines Agency Fimea & Social Insurance Institution, 2014). All forms of ADM and statins are prescribed by physicians and are not available as over-the-counter medication. ADM attracts more than the basic reimbursement, i.e. these drugs are reimbursed under Special Refund terms (Martikainen & Rajaniemi, 2002) and therefore purchases of ADM are particularly accurately recorded. Coverage in the Prescription Register of reimbursed medications prescribed by physicians is virtually complete for particular study period (Sund, Gissler, Hakulinen, & Rosén, 2014). From register data, time-related use can be calculated, and valid estimates of cumulative amounts made in connection with different types of medication. Medication duration in the current work is known for a longer time than in the majority of previous studies. Histories of previous operations which alter the risk of ovarian cancer are also reliable for the women in the cohort.

However, the epidemiological studies contain only information available on the registers. The registers lack data on laboratory examinations, family history, BMI, socioeconomic situation, aspects of lifestyle and reproductive factors. The severity of T2D and hypercholesterolaemia is not known because of the absence of laboratory examination results. However, DDDs of ADMs and insulin use correlate with both the duration and severity of T2D. Some life-style factors such as obesity, lack of exercise and poor diet are known risk factors of both T2D and breast cancer

(Kyu et al., 2016). In addition, obesity has been associated with poorer prognosis of ovarian cancer (Nagle et al., 2015) and breast cancer (Jiralerspong & Goodwin, 2016). Some of the unknown reproductive factors, such as nulliparity, late age at first pregnancy, late menopause and lack of breastfeeding are risk factors of both ovarian and breast cancer. However, it is not known whether these reproductive factors differ in women with T2D according to ADM use. Data on HRT, contraceptive use and over-the-counter drugs, which might also alter the risk of breast and ovarian cancers, are not included in the registers. In addition, information on whether or not the purchased medication was taken, is not known, but concordance between self-reported medication and information in the Prescription Register has been shown to be good (Haukka, Suvisaari, Tuulio-Henriksson, & Lönnqvist, 2007).

Much has been discussed about statin use and healthy user bias, as statin use is linked to healthy life-styles, adherence to treatments, better tolerance of side-effects and absence of contraindications (Beattie & Wijeysundera, 2010). However, statin users appear more likely to be elderly and have more coincident severe cardiovascular comorbidities than non-users of statins (C. C. Yang, Jick, & Testa, 2003). In a previous Finnish study on patients with newly diagnosed T2D (Vehko et al., 2013), statin use was slightly reduced in patients with lower incomes which supports the theory of healthy user bias.

Comorbidities are not recorded in the FinDM database adequately enough and were therefore not included in our study. Statins are linked to heart diseases (Vehko et al., 2013) and therefore related to mortality from causes other than cancer. However, in the study concerning the prognosis of ovarian cancer in women with T2D, mortality from causes other than ovarian cancer was low and therefore the lack of comorbidity data is unlikely to alter the study results notably. The FCR includes some information on cancer treatment given, but the data are not complete enough to be included in our study. However, national guidelines concerning ovarian and breast cancer treatment did not changed dramatically during the study period.

Challenges of confounding by indication are present in observational studies which contain endpoints that have not yet been studied in randomised controlled trials (Jorgensen, Sibley, & McClelland, 2013). As various types of medication are initiated to treat conditions other than the one in the focus of an observational study, differences in participants can have an impact on the results. As previously stated, underlying T2D and hypercholesterolaemia themselves alter the risks and prognoses of breast and ovarian cancer.

6.2 Association between antidiabetic medication and statin use and ovarian and breast cancer risk in women with T2D (Studies I and III)

The potential cancer-preventing influence of metformin in preclinical studies has led to several observational studies in this field, although many studies have had methodological shortcomings, such as time-related biases, as a result of their observational nature (Suissa & Azoulay, 2014). Because of the commonness of breast cancer, its incidence is more frequently studied than that of ovarian cancer.

In a previous study by Bodmer et al. (2011), a decreased incidence of ovarian cancer was reported in long-term metformin users, in contrast to our findings. In a study by Tseng (2015), a reduced incidence of ovarian cancer was noted among metformin users. Similarly to our study, both of these previous studies were register-based but lacked information on previous operations, and the diagnosis of ovarian cancer was not based on pathological diagnosis, unlike in our study. Although the database used in the study by Bodmer et al. was large, the actual number of ovarian cancer cases and metformin users remained small, which affects the reliability of the results. The sample size in Tseng's study was larger than ours; the results are remarkably clear in favour of metformin use. The incidence of ovarian cancer was up to 146.4 per 100,000 person-years in non-metformin users, while in our study, the incidence varied from 33.9 to 43.4 per 100,000 person-years between different ADM user groups. In our study, the first year after T2D diagnosis was excluded in order to reduce the risk of detection bias and reverse causality bias, but this was not done in the study by Bodmer et al. and in Tseng's study the exclusion criterion was follow-up duration less than 180 days, which is not adequate to avoid biases. In our study on ovarian cancer incidence the selected reference group for 'ever-users of metformin' was 'ever-use of other antidiabetic medication' which differs from previous studies in which the reference group has been 'never-users of metformin' (Bodmer et al., 2011; Tseng, 2015). Using 'never-users of metformin' as a reference group might lead to overestimation of the possible positive association between metformin and ovarian cancer incidence, because this reference group also includes insulin users, who are known to have hyperinsulinaemia and probably increasing cancer risk itself.

Our study is the first one to address the association between statin use and ovarian cancer risk in women with T2D. Although our study population was restricted to women with T2D, the study cohort is one the largest in terms of statin use and ovarian cancer risk. We did not find any evidence for an association

between statin use and the risk of ovarian cancer, which is in line with the results of the majority of previous studies (Baandrup et al., 2015; Desai et al., 2018; Lavie et al., 2013; Yu et al., 2009). In one of the previous studies have a decreased incidence of ovarian cancer among statin users was reported, but even in this study, the results were inconclusive when restricting the population to only women with T2D (Akinwunmi et al., 2019). In a few previous studies the number of women with T2D in their study populations have not been reported (Desai et al., 2018; Lavie et al., 2013), but 35.5% of statin users were women with T2D in a study by Yu et al.(2009) and 4.6% of ovarian cancer cases were in women with T2D in a study by Baandrup et al. (2015). In both studies, it is not possible to obtain results concerning only women with T2D. Similarly to our study, information on medication use has been register-based in the majority of studies (Baandrup et al., 2015; Lavie et al., 2013; Yu et al., 2009), but in few studies, medication use has been self-reported (Akinwunmi et al., 2019; Desai et al., 2018), which lowers the reliability of the results. To avoid reverse-causality bias, exposure to statins was considered to begin after one year of purchase in our study, which is similar in the studies by Yu et al. (2009) and Lavie et al. (2013), but in the study by Baandrup et al. (2015), statin users were defined as having two or more prescriptions and in the study by Akinwumni et al. (2019), the six months' use of statins was adequate. In addition, a few studies did not have adequate information on previous operations that lower the risk of ovarian cancer (Akinwunmi et al., 2019; Desai et al., 2018; Lavie et al., 2013).

Our study population concerning metformin use and breast cancer incidence is the second largest in this field. Contrary to our findings, the majority of previous studies have reported a lower incidence of breast cancer in women with T2D using metformin (Bosco et al., 2011; Chlebowski et al., 2012; Tseng, 2014), but in one study, the lower breast cancer incidence was seen only with long-term metformin use (Bodmer et al., 2010). On the other hand, a few studies have not found an association between metformin use and breast cancer incidence, similarly to our findings (Redaniel et al., 2012; Soffer et al., 2015). Breast cancer diagnosis was based on histological data obtained from a cancer registry in only one study (Bosco et al., 2011) besides our own. Information on actually purchased ADM was available in a few studies (Bosco et al., 2011; Soffer et al., 2015; Tseng, 2014), while other studies had information on prescriptions only (Bodmer et al., 2010; Redaniel et al., 2012), and in one study, information ADM used was self-reported only (Chlebowski et al., 2012). In addition, the duration of ADM use in some studies was not adequately reported (Chlebowski et al., 2012; Soffer et al., 2015),

while in other studies, classification as a metformin user required at least one year of medication use (Bodmer et al., 2010; Bosco et al., 2011; Tseng, 2014). In the study of breast cancer incidence, the selected reference group for 'ever-users of metformin' has been similar among previous studies, i.e. 'never-users of metformin' (Bodmer et al., 2010; Bosco et al., 2011; Tseng, 2014), although in some studies the reference group has included women without T2D (Chlebowski et al., 2012).

As insulin is considered to be a growth factor, the use of exogenous insulin can promote neoplastic growth (P. Home, 2013). Therefore, it is understandable that in epidemiological studies the use of insulin is associated with an increased risk of cancer in general (Currie et al., 2009). However, the results vary in studies on breast cancer risk. Insulin use was associated an increased risk of breast cancer in our study, in contrast to previous studies (Bodmer et al., 2010; Cleveland et al., 2012; Redaniel et al., 2012). When assessing insulin types separately, Habel et al. (2013) found an increased risk of breast cancer among glargine users, while most studies have not found such an association (Grimaldi-Bensouda et al., 2014; Kostev, 2012; Lind, Fahlen, Eliasson, & Oden, 2012; Suissa et al., 2011). However, these previous studies have been criticised as having high to moderate risks of bias, and inadequate power (Bronsveld et al., 2015).

In our study population, we did not find any evidence for an association between statin use and the risk of breast cancer. This is in line with the majority of previous studies on breast cancer (Beck et al., 2003; Borgquist et al., 2016; Boudreau et al., 2004; Boudreau et al., 2007; T. F. Chan et al., 2014; Coogan et al., 2002; Desai et al., 2013; Dumasia et al., 2006; Eaton, Eklof, Beal, & Sahmoun, 2009; Eliassen et al., 2005; Pocobelli et al., 2008; Setoguchi et al., 2007; Woditschka et al., 2010). However, some studies have reported a decreased incidence of breast cancer in lipophilic statin users (Cauley et al., 2006), or more precisely, in lovastatin users (Murakami et al., 2016). In contrast McDougall et al. (2013) found an increased risk of breast cancer in long-term (over 10 years) statin use. To our knowledge, our study is the first one focusing on the association between statin use and breast cancer incidence in women with T2D. Indeed, it is the first one to focus entirely on women with T2D. In only a minority of previous studies has information on coincident diabetes diagnosis been collected and in most of these studies the results have been adjusted accordingly (Borgquist et al., 2016; Boudreau et al., 2007; Eaton et al., 2009; Murakami et al., 2016), while some investigators have just reported the percentages of diabetes diagnoses in different medication groups (Desai et al., 2013). The accuracy of medication use is often not sufficiently adequate, and in many studies the medication purchases have been self-

reported only (Borgquist et al., 2016; Boudreau et al., 2004; Desai et al., 2013; Eliassen et al., 2005; McDougall et al., 2013; Pocobelli et al., 2008). In addition, the definition of a statin user has varied among the studies from one statin purchase or prescription to at least two years' use of medication. Although our study is focused on women with T2D as a subgroup of statin users, the sample size is relatively large in terms of breast cancer cases and the second largest in terms of statin users.

6.3 Prognosis of ovarian cancer in women with T2D using ADM and statins (Study II)

Our study has one of the largest study populations as regards metformin use and survival after ovarian cancer. Unlike our study, the results of some previous ones have indicated that metformin use has an association with a favourable prognosis of ovarian cancer in terms of OS or PFS (Bar et al., 2016; Kumar et al., 2013; Romero et al., 2012). However, the number of metformin users in these studies have been very low, varying from 12 to 61 women, and the studies have been based on single-institution data. The largest study on survival after ovarian cancer among metformin users was register-based and had similar inconclusive results as in our study owing to wide confidence intervals (Garcia et al., 2017).

Selection of the reference group in relation to metformin users affects interpretation of the results. The reference group for metformin users in our study was comprised of users of other types of oral ADM, while other studies have used non-users of metformin as the reference group. Furthermore, the reference group has also included women without T2D in some studies (Garcia et al., 2017; Kumar et al., 2013). This might lead to bias, as the prognosis of ovarian cancer has been suggested to be worse among women with T2D (Bakhru et al., 2011; Shah et al., 2014). In our opinion, users of other types of oral ADM represent the most relevant reference group when addressing the possible association between metformin and survival after ovarian cancer. Using 'no antidiabetic medication' as a reference definition could lead to bias, as persons with T2D without any proper medication would represent a selective group with some prognostic differences. In our study, metformin use was investigated three years before ovarian cancer diagnosis, while in some studies, the focus has been only on metformin use after ovarian cancer diagnosis (Bar et al., 2016; Kumar et al., 2013; Romero et al., 2012), and in one study, both pre- and postdiagnostic metformin use was investigated (Garcia et al., 2017). In some studies the time-varying nature of metformin treatment has not been

considered adequately, leading to a possible immortal time bias (Bar et al., 2016; Garcia et al., 2017; Romero et al., 2012). A major weakness in our study is the relatively short follow-up time (median 2.2 years), while in other studies the follow-up time has been from 32 to 63 months.

To our knowledge, our study is the first one in which the association between statin use and ovarian cancer prognosis in women with T2D has been explored. However, most previous investigators have reported coincident T2D and adjusted the results for T2D diagnosis (Bar et al., 2016; Couttenier et al., 2017; Verdoodt et al., 2017; Vogel et al., 2017). T2D has been diagnosed in 3─20.7% of women without statin use and in 15─29.4% among statin users. In all of these studies, the use of statins was clearly more common among women with T2D (Couttenier et al., 2017; Elmore et al., 2008; Habis et al., 2014; Verdoodt et al., 2017; Vogel et al., 2017). Statin use was associated with lower mortality from ovarian cancer in our study. Similarly, the majority of previous studies have reported a better overall survival in ovarian cancer patients who use statins (Couttenier et al., 2017; Elmore et al., 2008; Vogel et al., 2017). Contrary to this finding, some have not found an association with all-cause- or ovarian-cancer-specific mortality (Bar et al., 2016; Habis et al., 2014; Verdoodt et al., 2017). Most previous studies have been single-institution-based and have lacked adequate sample size, as the number of statin users has varied from 17 to 68 (Bar et al., 2016; Elmore et al., 2008; Habis et al., 2014; Lavie et al., 2013). A few previous studies have been register-based, similarly to ours, and the sample size has been greater than in our study (Couttenier et al., 2017; Verdoodt et al., 2017; Vogel et al., 2017). However, the classification of women as statin users has varied across all these studies. Some have been concentrated on statin use after ovarian cancer diagnosis (Bar et al., 2016; Habis et al., 2014) and some on both pre- and postdiagnostic use (Couttenier et al., 2017; Lavie et al., 2013; Verdoodt et al., 2017; Vogel et al., 2017), while we have focused on prediagnostic use. Our results are similar to those in most of the studies which have concerned prediagnostic statin use (Couttenier et al., 2017; Lavie et al., 2013; Vogel et al., 2017).

6.4 Prognosis of breast cancer in women with T2D using ADM and statins (Study IV)

Our study is the largest one in which association between metformin use and survival after breast cancer in women with T2D has been explored. Similarly to our study, some studies have reported an association between metformin use and

decreased all-cause mortality but not breast-cancer-specific mortality (Calip et al., 2015; Hou et al., 2013; Peeters et al., 2013; Xiao et al., 2014). A few studies have observed both better overall survival and lower mortality from breast cancer among metformin users (He et al., 2012; Kim et al., 2015). On the other hand, Lega et al. (2013) did not find an association between metformin use and mortality from either all-causes or breast cancer, while Vissers et al. (2015) observed lower mortality from breast cancer, but only in long-term metformin users.

In all of these previous studies the reference group in comparison with metformin users has been comprised of non-users of metformin, including women without appropriate ADM (Calip et al., 2015; He et al., 2012; Kim et al., 2015; Lega et al., 2013; Vissers et al., 2015; Xiao et al., 2014). In one study, the reference group also included women without diabetes (Hou et al., 2013). Differences in reference groups are also found in studies observing results similar results to ours. There are also some differences in study populations, as some investigators have concentrated only on older women (Lega et al., 2013), and some on specific breast cancer subtype (He et al., 2012; Hou et al., 2013; Kim et al., 2015; Xiao et al., 2014). Also, the duration of medication or cumulative use of metformin is not known in most of the previous studies (He et al., 2012; Hou et al., 2013; Kim et al., 2015; Xiao et al., 2014). Definitions of medication user vary, as in most studies only one prescription of metformin is enough to classify a woman as a metformin user (Calip et al., 2015; Lega et al., 2013; Peeters et al., 2013).

To our knowledge, there are only two previous studies on the association between statin use and breast cancer prognosis in women with T2D (Borgquist et al., 2019; Ceacareanu et al., 2011), and our study has the largest sample size in this field. Both of the previous studies have reported results similar to ours ─ prediagnostic statin use seems to be associated with lower mortality from breast cancer (Borgquist et al., 2019) and from all causes (Ceacareanu et al., 2011).

In most of the previous studies information on coincident T2D among statin users has been gathered, and in all studies, statin use has clearly been more common among women with T2D, the number of women with T2D varying from 4.5 to 34.1% in statin users compared with 1.1 to 7.5% in non-users of statins (Borgquist et al., 2019; Brewer et al., 2013; Cardwell et al., 2015; Desai et al., 2015; Mc Menamin, Murray, Hughes, & Cardwell, 2016; Nickels et al., 2013; Smith et al., 2016). In the majority of previous studies the results have been adjusted for T2D (Cardwell et al., 2015; Mc Menamin et al., 2016; Nickels et al., 2013; Smith et al., 2016). Most previous studies have not observed lower mortality from breast cancer and from other causes in statin users, in contrast to our findings (Brewer et al., 2013; Desai

et al., 2015; Nickels et al., 2013; Smith et al., 2016). On the other hand, some studies have reported lower mortality from both other causes and from breast cancer, similarly to our study (Borgquist et al., 2019; Mc Menamin et al., 2016; Murtola et al., 2014).

A few previous studies have explored the association between survival of breast cancer patients and postdiagnostic statin use only (Cardwell et al., 2015; Smith et al., 2016). Although all statin use might be affected by healthy-user bias, postdiagnostic statin use is more likely to be influenced by it because healthier patients are more likely to initiate or adhere to statin treatment after cancer diagnosis, and fatally ill cancer patients are more likely to stop statin usage, which is prescribed for primary or secondary prevention of cardiovascular events. In our study, only prediagnostic statin use was explored, but in the literature it has been observed that prediagnostic statin users are most likely to continue statin use after cancer diagnosis (Borgquist et al., 2019).

The major limitation of the study is the lack of information on biochemical prognostic factors of breast cancer. It was suggested in a preclinical study that statins might disrupt the synthesis of oestrogen via a cholesterol-lowering mechanism and therefore could be beneficial in ER-positive breast cancers (Nelson et al., 2013). However, previous epidemiological studies have not found an association between statin use, oestrogen status and survival of breast cancer patients (Mc Menamin et al., 2016; Smith et al., 2016).

6.5 Clinical implications and future research

There are two completed trials and five clinical trials with ongoing recruiting concerning metformin and survival after ovarian cancer. In these trials, metformin is mainly added to neoadjuvant or adjuvant chemotherapy, or to hormonal therapy. Interestingly, there are fewer ongoing clinical trials on statin therapy in connection with ovarian cancer; one concerns (hydrophilic) rosuvastatin and two involve (lipophilic) lovastatin and/or atorvastatin. There are over 40 clinical trials concerning metformin treatment and breast cancer. In addition, there are over 30 clinical trials on statins and breast cancer (Clinical trials, 2019).

On the basis of our study results, it would not be reasonable to initiate metformin or statin treatment solely in order to avoid ovarian or breast cancer development in a woman with T2D. However, the results suggest that tailoring of ADM might have far-reaching consequences not only for glycaemic control but also as regards cancer development, as insulin use in our study cohort was

associated with an increased incidence of breast cancer. Thus, it is known that insulin is required in T2D treatment in latter phases of the disease (also seen in our study results), due to the fact that insulin secretion decreases over time in patients with T2D (Zangeneh et al., 2006). In addition, insulin might be a third treatment option, and initiating insulin means a failure of earlier treatment or contraindication to other types of medication, which can be interpreted as a generally ill-health condition (Carstensen et al., 2012). Therefore, different characteristics of particular medication users might lead to unintentional selection bias in observational studies (Colhoun, 2009).

The possible role of lipophilic and hydrophilic statins on cancer development and prognosis should also be noted when prescribing statin medication for hypercholesterolaemia treatment. However, it is to be hoped that the results of clinical trials will expand our knowledge of both metformin and statin treatment in ovarian and breast cancer patients.

The FinDM database is an excellent source of material when conducting nationwide epidemiological studies on patients with T2D. It combines information from a variety of different registers that already exist. In the future, it will be important to form a new nationwide register for patients with diabetes that is more easily accessed and which also provides information not available in current registers. For example, the National Diabetes Register of Sweden has existed since the 1990s (Eliasson & Gudbjornsdottir, 2014). Luckily, the National Institute for Health and Welfare together with the Finnish Diabetes Association have initiated a plan to create a new register for diabetes and launch it in the near future (Jonsson & Niemi, 2019).

7 Conclusions

Based on the results of the present study, the following conclusions can be made:

1. No evidence of an association between metformin or statin use and ovarian cancer incidence was found in women with T2D.
2. Our findings are inconclusive as regards an association between metformin use and survival after a diagnosis of ovarian cancer in women with T2D. Some evidence was found that prediagnostic statin use might be associated with improved prognosis of ovarian cancer.
3. No evidence of an association between metformin or statin use and breast cancer incidence was observed in women with T2D. However, insulin use, especially cumulative use, was associated with an increased risk of breast cancer.
4. Reduced mortality from other causes was observed in breast cancer patients with T2D among metformin users compared with those using other types of oral ADM. However, findings are inconclusive as regards the association between metformin use and breast-cancer-specific mortality. Prediagnostic statin use seemed to reduce mortality from both breast cancer and from other causes in women with T2D.

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I Urpilainen, E., Marttila, M., Hautakoski, A., Arffman, M., Sund, R., Ilanne-Parikka, P., Arima, R., Kangaskokko, J., Puistola, U., Läärä, E., & Hinkula, M. (2018) The role of metformin and statins in the incidence of epithelial ovarian cancer in type 2 diabetes: a cohort and nested case-control study. *BJOG,* 125(8):1001-1008. doi: 10.1111/1471-0528.15151.

II Urpilainen, E., Marttila, M., Hautakoski, A., Arffman, M., Sund, R., Ilanne-Parikka, P., Arima, R., Kangaskokko, J., Puistola, U., Hinkula, M., & Läärä, E. (2018) Prognosis of ovarian cancer in women with type 2 diabetes using metformin and other forms of antidiabetic medication or statins: a retrospective cohort study. *BMC Cancer,* 18(1):767. doi: 10.1186/s12885-018-4676-z.

III Hosio, M.,* Urpilainen, E.,* Marttila, M., Hautakoski, A., Arffman, M., Sund, R., Puistola, U., Läärä, E., Jukkola, A., & Karihtala, P. (2019) Association of antidiabetic medication and statins with breast cancer incidence in women with type 2 diabetes. *Breast Cancer Research and Treatment,*175(3):741-748. doi: 10.1007/s10549-019-05185-0.

IV Hosio, M.,* Urpilainen, E.,* Hautakoski, A., Marttila, M., Arffman, M., Sund, R., Ahtikoski, A., Puistola, U., Karihtala, P., Jukkola, A., & Läärä, E. Survival in cases of breast cancer in women with type 2 diabetes using antidiabetic medication and statins: a retrospective cohort study. Manuscript.

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