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Lifestyle-related biomarkers and endometrial cancer survival: Elevated gamma-glutamyltransferase as an important risk factor

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ABSTRACT

Background: Lifestyle seems to play an important role in endometrial cancer mortality, but it remains unclear which biomarkers are involved. The aim of this study was to assess the extent of the association between lifestyle-related biomarkers and the survival of endometrial cancer patients. *Methods*: A subcohort of 242 endometrial cancer patients, from a population-based study of the more than 90,000 female participants of the Vorarlberg Health Monitoring and Promotion Programme, was followed for a median duration of twelve years. Besides age, tumour staging, and histology, also pre-diagnostic levels of body mass index, blood pressure, triglycerides, total cholesterol, glucose, gamma-glutamyltransferase (GGT), and serum uric acid were analysed in Cox proportional hazards regression models to estimate multivariate mortality risks. *Results*: During follow-up 89 deaths occurred of which 49 were cancer-related. Survival was associated with age, tumour stage, and histology. Of the biomarkers, $\log_{10}$-transformed GGT showed a large effect on cancer-related mortality (HR = 3.35, 95% CI 1.12–10.03), whereas the other parameters did not appear with significant effects after adjustment for the other factors. *Conclusion*: Elevated level of GGT, a lifestyle-related marker, was associated with poor survival among endometrial cancer patients.

1. Introduction

Endometrial cancer is the sixth most common incident cancer in women worldwide, with an age-standardised incidence of 8.2 per 100,000 women per year. In Western Europe and North America the rates are higher with 11.2 and 16.4 per 100,000 respectively [1]. Recent 5-year relative survival in the United States of America is estimated at about 80% overall [2], but decreases dramatically for advanced stages. Most endometrial carcinomas are adenocarcinomas [3] and staged surgically with the FIGO system [4]. Commonly treatment involves surgery and, in an adjuvant setting, chemotherapy, radiotherapy or a combination of both [5]. The incidence of this cancer type is known to be clearly positively associated with obesity [6], but risk factors also include increasing age, unopposed oestrogen therapy, nulliparity, diabetes, and hypertension [7]. However, the specific determinants of patients' survival is still widely unexplored and the role of lifestyle only beginning to become unravelled.

Cancer mortality in general has been associated with lifestyle-related factors like smoking and nutrition, but there is evermore interest in lifestyle-related biomarkers, for aetiological and for prognostic reasons. For example, an association has been reported between elevated gamma-glutamyltransferase (GGT) and general cancer mortality from a USA population study [8]. GGT seems to be involved in tumour progression by oxidative stress pathways [9–11] and it is a marker of excessive alcohol intake [12]. Alcohol consumption, metabolic factors, and oxidative stress have been linked to the cancer process [13].

High blood pressure, high blood glucose, overweight, and high cholesterol are among the most important risk factors related to overall mortality worldwide and probably involved in a large amount of cancer deaths [14]. In the Me-Can project several of these metabolic factors were found to be associated with mortality from specific cancers [15,16]. Specifically, fatal uterine corpus cancer was related to body mass index and to a lesser extent associated with blood pressure, glucose and triglycerides [17]. Furthermore, in a review of the associations of serum uric acid and GGT, these two metabolic and oxidative stress markers also

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appeared to be independent factors involved in cancer incidence, with elevated levels related to higher cancer risks [18].

The potential effect of lifestyle-related biomarkers, particularly on the survival of endometrial cancer patients, is still unclear. Recently, a retrospective multi-centre study did actually find a doubled mortality risk of endometrial cancer patients with elevated GGT levels, but unfortunately no other lifestyle factors were included in the analyses [19]. Our study data includes more pre-therapeutically measured markers of endometrial cancer patients, that is body mass index, hypertension, triglycerides, total cholesterol, glucose, GGT and serum uric acid, all of which are linked to long-term behavioural patterns. The aim of the present study was to simultaneously investigate, to our knowledge for the first time, the association of these lifestyle-related biomarkers with the overall survival and the cancer-related mortality of endometrial cancer patients.

2. Materials and methods

2.1. Study population

The endometrial cancer patients of this study are a sub-cohort from the Vorarlberg Health Monitoring and Promotion Programme (VHM&PP) in which longitudinal health examination data in relation to cardiovascular and cancer events have been prospectively gathered for more than 25 years. VHM&PP is one of the world's largest population-based risk factor surveillance programmes [20] and several general relationships of body mass index, glucose, triglycerides, cholesterol, GGT, and serum uric acid with cancer have already been reported [18,21–24]. Since 1985 all adults in the region were invited to participate and repeated routine health examinations are subsequently performed by trained physicians. Follow-up included the gathering of death certificate data, based on a well established system with high rates of autopsies. Informed consent was obtained from all participants at each examination visit and the relevant research ethical committee has given its approval (Ethikkommission des Landes Vorarlberg, EK-Nr. 2006-6/2).

2.2. Patients and measurements

Among the 94,805 female participants of VHM&PP included in the programme between 1985 and 2003, we extracted the sub-cohort of 318, histologically confirmed, primary endometrial cancer cases (ICD-10 C54.1), thus without any earlier carcinoma episode. Of these, only 242 patients were included in the current study because they had an exposure measurement of less than 5 years before the cancer diagnosis (of these 242 participants, 48% had a diagnosis within one year after the examination and 71% within two years). Information was available on pre-diagnostic levels of body mass index, systolic and diastolic blood pressure, triglycerides, total cholesterol, glucose, GGT (measured at 37 °C), and serum uric acid as the baseline measurement. Due to their non-normal distribution, triglycerides, and GGT were $\log_{10}$-transformed. When GGT was categorised, the cut-off level was set at 18.0 U/l (upper normal level). Following World Health Organization and International Society of Hypertension [25], we defined hypertension by systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg. The follow-up for the current study ended with emigration or loss to follow-up, at death, or at the end of the study period on 31st December 2009.

2.3. Statistical analysis

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and the accompanying 95% confidence intervals (CIs). We investigated overall and cancer-related mortality, first by applying univariate models resulting in crude estimates. In addition, a Kaplan–Meier plot was constructed to reveal the univariate effect of GGT on cancer-related mortality and the difference between categories was tested with a logrank test. Secondly, we calculated restricted multivariate models of one biomarker adjusted for the known relevant risk factors age, tumour-staging (FIGO) and histology, together with the examination year. Finally, a full model of all variables was fitted, including body mass index, hypertension, triglycerides, total cholesterol, glucose, GGT, and uric acid simultaneously. In the regression models age and examination year were rescaled to attain risk estimates per unit of 10 years. The histology subgroup of serous and clear cell tumours among the adenocarcinoma did not show different risk estimates, so it is not considered separately in the results. Also, since for several patients the histology was unknown, a sensitivity analysis was conducted to compare the multivariate results of all-cause mortality with and without this subgroup. Furthermore, in a separate analysis effect modification of FIGO stage on the association between GGT and mortality was tested by adding an interaction term in the models, but no significant effect was found.

Missing data among some biomarker measurements were imputed since this is to be preferred to complete case analysis with fewer cases [26]. Imputation was performed using the median level of the other patients [27]. In a comparison of the results with and without imputation the estimates hardly changed, only the precision differed. A two-sided p-value of less than 5% was considered as statistically significant. The statistical analyses were performed with SPSS 17.

3. Results

3.1. Patients

The 242 study participants were between 35 and 90 years old at the time of diagnosis, with a mean of 61 years. Table 1 shows details of the women's distributions of the variables body mass index, blood pressure, triglycerides, total cholesterol, glucose, GGT, and serum uric acid. A third of the patients were obese, two thirds had hypertension, two thirds showed a high level of triglycerides, 43% had high cholesterol values, 14% had high glucose levels,

Table 1
Baseline characteristics of the study participants ($n = 242$).

	Average	n
Age (years)	61.0 (9.8)[a]	
Body mass index (kg/m^2)	28.5 (5.8)[a]	
≥30 kg/m^2		82 (34%)
Blood pressure (mmHg)		
Systolic	145 (22)[a]	
Diastolic	86 (12)[a]	
SBP ≥ 140 or DBP ≥ 90 mmHg		168 (69%)
Triglycerides[b] (mg/dl)	124 (90–173)[c]	
≥100 mg/dl		159 (66%)
Total cholesterol[b] (mg/dl)	236 (44)[a]	
≥240 mg/dl		103 (43%)
Glucose (mg/dl)	102 (34)[a]	
≥126 mg/dl		34 (14%)
GGT[b] (U/l)	23.3 (17.9–32.2)[c]	
≥18.0 U/l		171 (71%)
Serum uric acid[d] (mg/dl)	5.06 (1.30)[a]	
≥6.0 mg/dl		47 (22%)

DBP: diastolic blood pressure; GGT: gamma-glutamyltransferase; n: number; SBP: systolic blood pressure.
[a] Mean (standard deviation).
[b] Missing value: $n = 1$.
[c] Median (inter-quartile range).
[d] Missing value: $n = 24$.

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Table 2
Clinicopathological parameters and follow-up data of the study participants ($n = 242$).

FIGO stage, *n* (%)	
I	164 (68%)
II	50 (21%)
III or IV	28 (12%)
Histology, *n* (%)	
Adenocarcinoma	189 (78%)
Adenosquamous carcinoma	16 (7%)
Squamous cell carcinoma	1 (0%)
Unknown	36 (15%)
Follow-up (years)	
Median (IQR)	11.9 (7.3–16.3)
Total	2861 person-years
Deaths, *n* (%)	
All-cause	89 (37%)
Cancer-related	49 (20%)
Related to cancer of the genital organs	41 (17%)

IQR: inter-quartile range; *n*: number.

almost three quarters appeared with high or elevated GGT levels, and among a fifth of the patients hyperuricaemia was an issue. About two thirds of the patients were classified in FIGO stage I, 21% in stage II, and 12% in stages III and IV combined (Table 2). Regarding histology, more than three-quarters concerned adenocarcinoma and 7% adenosquamous carcinoma. During 2861 person-years of follow-up, on average nearly 12 years per participant, 89 all-cause and 49 cancer-related deaths occurred, of which 28 were malignant neoplasms of genitourinary organs (ICD-9 179-189), 13 of female genital organs (ICD-10 C51-C58), and 8 non-genital.

3.2. All-cause mortality

In the univariate analyses of all-cause mortality, age, stage, and histology showed significant effects (HR = 2.13 [95% CI 1.71–2.65], HR = 2.48 [95% CI 1.90–3.22], HR = 2.17 [95% CI 1.07–4.39], and HR = 2.85 [95% CI 1.77–4.60] respectively), which also applied for hypertension (HR = 2.30, 95% CI 1.34–3.95), triglycerides (HR = 4.00, 95% CI 1.51–10.55), and GGT (HR = 2.51, 95% CI 1.24–5.10) (Table 3). In the restricted models, with adjustment for age, year, stage and histology, the risk estimates of hypertension (HR = 1.51, 95% CI 0.87–2.60), and triglycerides (HR = 1.40, 95% CI 0.48–4.05) were no longer significant, whereas GGT still had a more than two-fold mortality risk per $\log_{10}$-unit elevation (HR = 2.28, 95% CI 1.04–5.02). In the full multivariate model, adjusting for all covariates simultaneously, the effects of age, stage, and histology were retained in comparison to the univariate results. The GGT effect also changed only marginally after adjustment for all covariates (HR = 2.37, 95% CI 1.01–5.56).

3.3. Cancer-related mortality

For cancer-related mortality, age showed a significant univariate effect (HR = 1.55, 95% CI 1.16–2.08), as did stage (HR = 3.16, 95% CI 2.25–4.45) and the "squamous cell carcinoma/unknown" category of histology (HR = 4.66, 95% CI 2.59–8.39) (Table 4). GGT (HR = 3.01, 95% CI 1.20–7.57) also showed a significant univariate effect (Fig. 1). In the restricted model the GGT effect estimate stayed at the same level (HR = 3.27, 95% CI 1.17–9.19). After adjustment for all covariates the associations of age and histology remained, but FIGO stage showed a weaker effect (HR = 2.72, 95% CI 1.88–3.95): an almost three-fold risk for FIGO stage II and a more than seven-fold risk for the higher stages (stage III and IV combined), compared to the reference. For GGT also a significant effect was found (HR = 3.35, 95% CI 1.12–10.03). When categorising GGT into groups with 18 to <36 and ≥ 36 U/l, compared to the group <18 U/l as the reference, the adjusted estimates were HR = 2.03 (95% CI 0.84–4.93) and HR = 3.03 (95% CI 1.10–8.30) respectively. The multivariate effect of increasing ($\log_{10}$-transformed) GGT levels on the cancer-related mortality risk, with the GGT level of 5 U/l as the reference (relative risk of 1.00) is shown in Fig. 2.

4. Discussion

In this large-scale population-based study the effect of the biomarkers body mass index, hypertension, triglycerides, cholesterol, glucose, GGT, und uric acid was investigated, to our knowledge for the first time, simultaneously in relation to endometrial cancer survival. Beside some significant univariate associations, the relation between GGT and mortality remained statistically significant after adjustment, pointing to an independent effect of GGT on survival of endometrial carcinoma patients. GGT exhibited a tripled risk per $\log_{10}$-unit increase of cancer-related mortality (e.g. from 5 to 50 U/l or from 10 to 100 U/l). Furthermore, age, FIGO stage, and histology were important factors.

4.1. Gamma-glutamyltransferase

The finding of an association between GGT and endometrial cancer survival was also reported by Seebacher et al., although

Table 3
Crude and adjusted risk estimates of all-cause mortality.

Exposure	Univariate models HR (95% CI)	Restricted multivariate models[a] HR (95% CI)	Full multivariate model HR (95% CI)
Age (years), per 10 years	2.13 (1.71–2.65)		2.18 (1.69–2.82)
Examination year, per 10 years	0.79 (0.49–1.26)		0.68 (0.40–1.16)
FIGO stage (stage I = ref)[b]	2.48 (1.90–3.22)		2.19 (1.62–2.94)
Histology (adenocarcinoma = ref)			
Adenosquamous carcinoma	2.17 (1.07–4.39)		2.09 (0.89–4.89)
Squamous cell carcinoma/unknown	2.85 (1.77–4.60)		3.07 (1.78–5.29)
Body mass index (kg/m^2)	1.028 (0.994–1.063)	0.989 (0.953–1.025)	0.974 (0.933–1.017)
Hypertension (yes vs. no)	2.30 (1.34–3.95)	1.51 (0.87–2.60)	1.54 (0.85–2.76)
$\log_{10}$(Triglycerides) (mg/dl)	4.00 (1.51–10.55)	1.40 (0.48–4.05)	1.16 (0.36–3.71)
Total cholesterol (mg/dl)	1.001 (0.997–1.006)	1.000 (0.996–1.005)	0.999 (0.993–1.004)
Glucose (mg/dl)	1.005 (0.999–1.010)	0.998 (0.992–1.004)	0.997 (0.990–1.003)
$\log_{10}$(GGT) (U/l)	2.51 (1.24–5.10)	2.28 (1.04–5.02)	2.37 (1.01–5.56)
Serum uric acid (mg/dl)	1.159 (0.977–1.376)	1.067 (0.906–1.258)	1.064 (0.904–1.253)

CI: confidence interval; HR: hazard ratio; GGT: gamma-glutamyltransferase; ref: reference.
[a] Models containing the biomarker in question adjusted for age, examination year, stage, and histology.
[b] Categories: stage I (ref), stage II, and stages III and IV combined.

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Table 4
Crude and adjusted risk estimates of cancer-related mortality.

Exposure	Univariate models HR (95% CI)	Restricted multivariate models[a] HR (95% CI)	Full multivariate model HR (95% CI)
Age (years), per 10 years	1.55 (1.16–2.08)		1.53 (1.09–2.15)
Examination year, per 10 years	1.25 (0.68–2.29)		1.14 (0.57–2.27)
FIGO stage (stage I = ref)[b]	3.16 (2.25–4.45)		2.72 (1.88–3.95)
Histology (adenocarcinoma = ref)			
Adenosquamous carcinoma	1.48 (0.45–4.90)		1.31 (0.34–5.12)
Squamous cell carcinoma/unknown	4.66 (2.59–8.39)		4.48 (2.25–8.91)
Body mass index (kg/m^2)	1.021 (0.975–1.068)	0.980 (0.932–1.031)	0.963 (0.906–1.024)
Hypertension (yes vs. no)	1.89 (0.94–3.79)	1.39 (0.67–2.87)	1.44 (0.67–3.10)
$\log_{10}$(Triglycerides) (mg/dl)	2.34 (0.62–8.88)	1.31 (0.31–5.63)	0.90 (0.17–4.63)
Total cholesterol (mg/dl)	1.000 (0.994–1.006)	1.002 (0.995–1.008)	1.001 (0.994–1.008)
Glucose (mg/dl)	1.005 (0.998–1.012)	1.001 (0.993–1.010)	1.000 (0.992–1.009)
$\log_{10}$(GGT) (U/l)	3.01 (1.20–7.57)	3.27 (1.17–9.19)	3.35 (1.12–10.03)
Serum uric acid (mg/dl)	1.105 (0.879–1.390)	1.052 (0.838–1.319)	1.072 (0.857–1.341)

CI: confidence interval; HR: hazard ratio; GGT: gamma-glutamyltransferase; ref: reference.
[a] Models containing the biomarker in question adjusted for age, examination year, stage, and histology.
[b] Categories: stage I (ref), stage II, and stages III and IV combined.

their study was done without adjustment for other biomarkers [19]. They focused on the association between GGT (≥36.00 versus ≤35.99 U/l) and progression-free survival and found a significant doubled risk, after adjustment for age and clinicopathological parameters.

Our finding does not imply causation, although the temporal sequence of events is reassuring with GGT measurement before the start of the analysis period in which the patient was at risk. Also, experimental models have elucidated the ability of cellular GGT to modulate crucial redox-sensitive functions, such as antioxidant/antitoxic defences and cellular proliferative/apoptotic balance, and its role in tumour progression, invasion, and drug resistance has been proposed [9–11]. Furthermore, the impact of GGT on the incidence, metastasis, and recurrence of various malignancies is increasingly becoming evident [18,28,29].

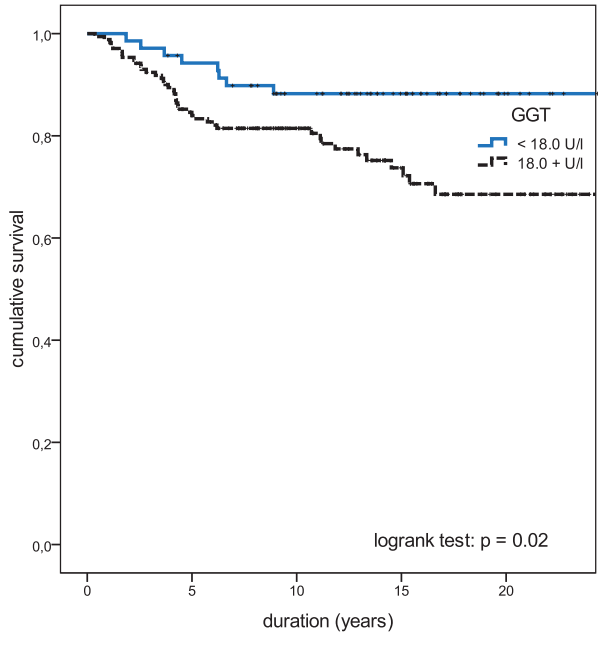

Fig. 1. Kaplan–Meier survival plot of cancer-related mortality by gamma-glutamyltransferase (GGT).

In the context of lifestyle, GGT is a biomarker for adverse alcohol consumption [12] and it is associated with metabolic factors such as hyperglycaemia [30–32], dyslipidaemia [33], and obesity [34]. Physical activity is able to reduce serum levels of GGT [34]. In addition, Breitling et al. reported relations between smoking and GGT, modified by alcohol consumption and body mass index [35]. Lee and Jacobs stated that GGT can be seen as a biomarker of exposure to certain cancer-causing xenobiotics, including persistent organic pollutants [36]. Altogether, GGT is closely associated with lifestyle and environmental conditions. In our study an independent relation to cancer-related mortality was observed, whereas we did not find evidence of an effect of the other lifestyle biomarkers.

4.2. Health condition

In the current study significant univariate associations with mortality were seen for hypertension and triglycerides, besides

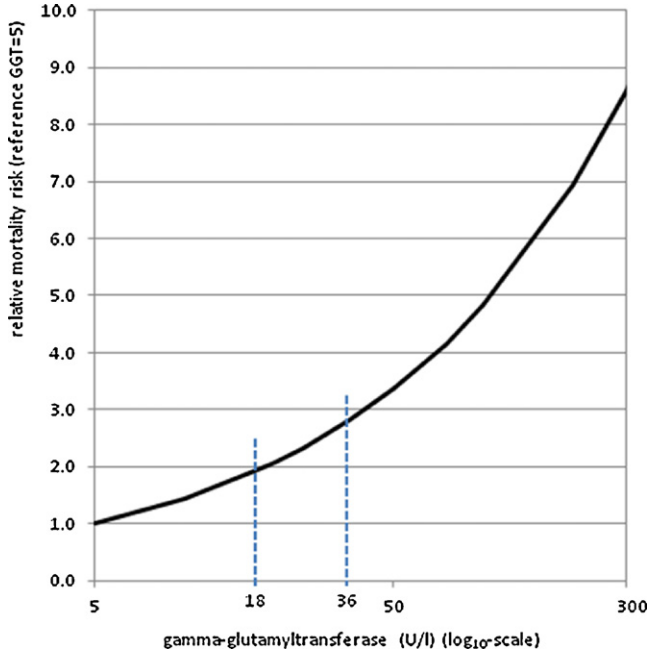

Fig. 2. Relation between gamma-glutamyltransferase (GGT) and cancer-related mortality[a].
[a] Adjusted for all the covariates (see Table 4); GGT reference values of 18 and 36 U/l inserted on the horizontal axis with actual GGT-values on a logarithmic scale.

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GGT. Hypertension was also reported to be common among endometrial cancer patients in a cohort study based in Ohio [37] and has been shown to be associated with an increased risk of cancer mortality in general [38]. In the large population-based Me-Can cohort study, elevated systolic and diastolic blood pressure were found to contribute significantly to higher risks of fatal uterine corpus cancer, with adjustment for several (metabolic) covariates [17]. Increasing body mass index and obesity have also been linked to endometrial cancer incidence [6,21]. Furthermore, overweight is believed to play a major role in the pathogenesis of endometrial cancer and is closely associated with other medical co-morbidities like diabetes mellitus and hypertension. As von Gruenigen et al. stated, endometrial cancer survivors often have unhealthy lifestyles with unfavourable consequences [37]. We also found the patients in this study in a bad condition with adverse clinical findings at baseline. Important behavioural components are involved here and these give opportunities for interventions. It has been suggested that evidence-based primary preventive efforts could potentially avoid maybe half of all cancer deaths every year [39]. Evermore research on physical activity has made it apparent that better health and wellbeing of cancer survivors in general is achievable [40]. Even a simple intervention of 30 minutes of moderate physical activity every day would be beneficial for survival [41]. Moreover, as Courneya et al. have pointed out, it would also contribute to improvements in quality of life [5]. However, when considering the lifestyle-related factors simultaneously in our study, only the GGT effect persisted. This gives reason to believe that, apart from clinicopathological factors, lifestyle factors primarily linked to GGT are involved in endometrial carcinoma survival and the other biomarkers do not exert an independent effect.

Fentiman has recently pointed out that it is uncertain whether GGT is directly involved in the progression of cancer in an aetiological sense or that it should be seen as an "indicator of collateral damage" [42]. In either case there would seem to be therapeutic options concerning lifestyle changes for endometrial cancer patients. Regular monitoring of GGT during therapy and at follow-up investigations might additionally motivate patients to improve their lifestyle.

4.3. Strengths and limitations

Strengths of our study are a prospective design of a large endometrial cancer cohort, a long follow-up period, and well-documented data. On the other hand we faced several limitations like the lack of information on surgical and adjuvant treatment and no data on anti-hypertensive treatment at baseline or before. Therefore, we could not adjust for use of hypertensive drugs at time of the diagnosis. Because some women may thus have been categorised as non-hypertensive, this might have led to a dilution of an existing hypertension effect. Furthermore, the effect of long-term anti-hypertensive treatment on cancer mortality is unclear, with inconsistent claims of negative, no, and positive associations between various types of such drugs and cancer [43]. In addition, our data on histology was not complete and we had to adjust for this variable with an "unknown"-category. The histology has thus not been fully incorporated, but a sensitivity analysis suggested the bias to be negligible (HR = 1.96 [95% CI 0.75–5.08], when excluding the cases of the third histology category, versus HR = 2.37 [95% CI 1.01–5.56]). Also, exposure measurement was not at diagnosis but the last one before, up to 5 years earlier. On inspection, the levels of the biomarkers did not appear to vary according to the length of time between measurement and diagnosis, indicating stability of the levels. Another limitation of our study is the rather small number of cancer-related deaths as the outcome. For this reason all-cause mortality was also considered. Although the statistical power of the cancer-related events analysis was limited, the results of both outcomes are plausible and consistent, so it appears only the precision of the estimates are compromised.

5. Conclusion

In conclusion, in our data elevated GGT levels were independently associated with poor survival in patients with endometrial cancer, next to increasing age, advanced tumour stage, and adverse histology. As this factor is modifiable through healthy behaviour, endometrial cancer patients might enhance their life expectancy by adapting their lifestyle, though this beneficial effect has to be replicated in a larger prospective trial.

Conflict of interest statement

None.

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