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Metabolic risk factors and cervical cancer in the Metabolic Syndrome and Cancer Project (Me-Can)

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Abstract

Background Little is known about the association between metabolic risk factors and cervical cancer carcinogenesis.

Material and methods During mean follow-up of 11 years of the Me-Can cohort (N= 288,834) 425 invasive cervical cancer cases were diagnosed. Hazard ratios (HRs) were estimated by use of Cox proportional hazards regression models for quintiles and standardized z-scores (with a mean of 0 and a SD of 1) of BMI, blood pressure, glucose, cholesterol, triglycerides and MetS score. Risk estimates were corrected for random error in the measurements.

Results BMI (per 1SD increment) was associated with 12%, increase of cervical cancer risk, blood pressure with 25% and triglycerides with 39%, respectively. In models including all metabolic factors, the associations for blood pressure and triglycerides persisted. The metabolic syndrome (MetS) score was associated with 26% increased corrected risk of cervical cancer. Triglycerides were stronger associated with squamous cell carcinoma (HR 1.48; 95% CI, 1.20-1.83) than with adenocarcinoma (0.92, 0.54-1.56). Among older women cholesterol (50-70 years 1.34; 1.00-1.81), triglycerides (50-70 years 1.49, 1.03-2.16 and ≥ 70 years 1.54, 1.09-2.19) and glucose (≥ 70 years 1.87, 1.13-3.11) were associated with increased cervical cancer risk.

Conclusion The presence of obesity, elevated blood pressure and triglycerides were associated with increased the risk of cervical cancer.

Highlights: Elevated BMI, blood pressure and triglycerides levels are associated with increased cervical cancer risk. A combined score of the MetS is associated with increased cervical cancer risk. Associations differ by histological subtype of cervical cancer.

Introduction

Cervical cancer is the third most frequent cancer in women worldwide and the leading cause for cancer mortality predominantly in women from developing countries (1). The global burden of obesity and its complications is rising (2), which may also have implication for cancer risk. Most cancers (about 80%) of the uterine cervix are squamous cell carcinoma (SCC). Due to cervical cytology screening the proportion of adenocarcinoma (ADC) has increased to 10-15% during the past decades (3). Infections with certain human papillomavirus (HPV) strains 16 and 18 are the major risk factor for cervical cancer (3)(4). More than 150 HPV types have been reported, of which about 40 can infect the cervix (5). Worldwide the contribution of HPV 16 and 18 was estimated at about 63 % of all cervical cancers (6)(7). HPV infections are often acquired in younger age and persistence of HPV infections are virtually observed in all cervical cancer cases (5). HPV 18 was more common in ADC than SCC cases and was associated with lower age for women with cervical cancer (6). Other risk factors include long-term use of oral contraceptives, parity, and smoking (8). The etiology of ADC may differ from that of SCC (9)(10) concerning smoking (11), while both entities share risk factors related to reproductive and sexual behavior (12)(13)(14). Thus, differential association with other factors such as the metabolic syndrome (MetS) can be hypothesized.

The MetS is characterized by obesity, hyperglycemia, dyslipidemia and hypertension and has been shown to increase risk of several common cancer types (15). Results from previous epidemiological studies have shown associations between some metabolic factors and cervical cancer risk (10)(16)(17)(18), for example serum triglyceride levels and systolic blood pressure were positively associated with cervical cancer risk (17)(18)(19). Adipose tissue is an endocrine organ producing hormones and proteins e.g. estrogen and adipokines. Immunological alterations are commonly seen in metabolic disease (20). For estrogen,

adipokins and cytokines associations with cervical cancer have been reported (21),(22) suggesting that metabolic factors could play a role as co-factors in the cancerogenesis of cervical cancer. However, little is known about the associations between metabolic factors - individually and combined- and the risk of cervical cancer risk.

The aim of this study was to assess the associations between metabolic factors (both individually and combined) and the risk of cervical cancer by subtype in the large prospective Metabolic syndrome and Cancer project (Me-Can).

Material and methods

Study population

The Me-Can study design, participating cohorts and data collection procedures have been described in detail previously (23)(24). Briefly, for Me-Can studies data from several long-standing cohorts in Austria (the Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), Norway (the Norwegian Counties Study (NCS), the Cohort of Norway (CONOR) and the Age 40 programme (40-y)) and Sweden (the Västerbotten Intervention Project (VIP) and the Malmö Preventive Project (MPP)) were pooled. All participating cohorts were set up as part of population-based surveillance/screening programmes for the prevention of chronic diseases such as cardiovascular disease or cancer (23), and included at least one health examination, during which height, weight, and systolic and diastolic blood pressure had been measured. Blood concentrations of glucose, total cholesterol and triglycerides were quantified and information on smoking status recorded. Across sub-cohorts anthropometric measurements were conducted in a similar way, with participants wearing light indoor clothes and no shoes. Between sub-cohorts blood pressure measurement protocols differed according to resting time prior to measurement, body position and equipment. Also fasting time before blood withdrawal differed by cohorts. For the present analysis data of 288,834 women collected between 1974 and 2005 were used. Incident cases of cancers of the cervix (International Classification of Diseases, seventh revision (ICD-7:

171)) were identified through linkages with the national cancer registries. Cervical cancers were classified by histological type (25). Data on vital status were obtained from mortality registries. To reduce the possibility of reverse causation, follow-up started one year after the baseline examination. Thus, the analytic cohort comprised 288,274 women, among whom 425 cervical cancer cases have been identified. Person-years under observation for each person were calculated until the date of diagnosis, migration or the date of death, whichever came first. Participants were censored by December 31, 2003 in Austria, 2005 in Norway and 2006 in Sweden, respectively.

Statistical analysis

Cox proportional hazards regression models with age as the time variable were fitted to obtain hazard ratios (HRs) with 95% confidence intervals (CIs) for cervical cancer. Quintile cut-points were determined for BMI, mid blood pressure [(systolic blood pressure + diastolic blood pressure)/2], glucose, cholesterol, and triglycerides within the six sub-cohorts, and for glucose, cholesterol and triglycerides, also in categories of fasting time (fasting; < 4, 4-8, and ≥ 8 hours). The models were stratified for cohort (six sub-cohorts) and for year of birth (five categories; ≤ 1929 , 1930-9, 1940-9, 1950-9 and ≥ 1960) and adjusted for smoking status (four categories; never, former and current smokers, unknown). Additional models were calculated adjusting for BMI and models including all metabolic factors simultaneously. Test for trend was based on the Wald test for linear regression assigning the risk estimate of each quintile to the median exposure levels within the Me-Can cohort.

The variables BMI, mid blood pressure, glucose, cholesterol, and triglycerides were standardized to a z-score variable with mean = 0 and SD = 1. The variables were standardized separately for the six sub-cohorts, for glucose, cholesterol, and triglycerides also for fasting time. Since glucose and triglycerides were skewed and had outliers, they were log-

transformed before standardization. A score for the MetS was constructed by adding the individual z-scores and standardized separately for the six sub-cohorts and for fasting time. Analyses were performed separately for SCC and ADC of the uterine cervix. Information on age of menopause was not available for most women; therefore we used attained age of 50 years as proxy for menopausal state. Stratified analyses were performed by attained age: <50, 50-69 and ≥ 70 years.

We tested for interactions between the z-scores for blood pressure, glucose, cholesterol and triglycerides and BMI group by likelihood-ratio tests for the product term of MetS factors in the corresponding model. Two-sided p-values of 0.05 were considered statistically significant. All calculations were carried out with the statistical software package SAS release 9.2 (SAS Institute, Cary, N.C.; USA) and R (version 2.7.2) for random error calibration.

Correction of the measurement error

In order to account for the measurement error of the different exposures and their variation during follow-up, corrections have been made by calculation of the regression dilution ratio (RDR) and by applying the regression calibration method (26). In brief, based on the data of 133,820 subjects with repeated health examinations comprising 406,364 observations in the Me-Can cohort, calibrated values were calculated by linear mixed effects models that considered age at baseline, fasting time, smoking status, sex, and time from baseline to repeated measurement as fixed effects and cohort as random effect (27). Only repeated measurements with the same fasting time and in the same as the original cohort with information on smoking status were used. Mean time since the baseline measurement was 6.9 (SD 3.9) years. Corrections of the HRs for RDR were obtained by $\exp(\log(\text{HR})/\text{RDR})$. The sex-specific RDR used in the analysis were: BMI 0.90, blood pressure 0.56, blood glucose 0.27, total cholesterol 0.66, and triglycerides 0.50.

1 The second correction method refers to the regression calibration model (RC). The exposure
2 of interest as measured was replaced by a predicted value calculated by a regression model
3 with age at baseline, fasting time, smoking status and time from baseline as fixed and cohort
4 as random effect (28). Regression calibration method was used in fully adjusted models, since
5 it allows correction of random error in measurements also for covariates.

6 7 **Results**

8 In the Me-Can cohort, mean age at measurement was 44.1 (SD 12.3) years and mean follow-
9 up time was 11.3 (SD 6.8) years (Table 1). Among women with at least one year of follow-up,
10 a total of 425 cases of cervical cancer occurred. Information on histology was available for all
11 cases: 337 (79%) cases with SCC, 59 (14%) cases of ADC, and 29 (7 %) cases with other
12 histologic types have been registered. Mean age at diagnosis was 50.5 (SD 11.3) years for all
13 cervical cancer cases combined and 50.5 (11.1) years for SCC, 49.1 (10.6) years for ADC,
14 and 54.4 (14.3) years for cases with other histologic types.

15 We first examined the risk of cervical cancer by quintiles of the individual metabolic factors
16 (table 2). Compared with the 1st quintile, high levels (5th quintile) of triglycerides were
17 associated with increased risk of cervical cancer 2.80 (95%CI, 1.44-5.46). Increased risk of
18 cervical cancer was observed for high levels of BMI and blood pressure, but no other MetS
19 components were statistically significantly associated with the risk of cervical cancer.
20 However, the test for linearity reached borderline significance for BMI, blood pressure and
21 triglycerides (p-values: 0.06, 0.08 and 0.06, respectively).

22
23 Table 3 shows the hazard ratios of cervical cancer for 1 SD increase in the standardized z-
24 scores of MetS and its components. The MetS score was associated with increased risk of
25 cervical cancer (HR, 1.26; 95% CI, 1.09-1.47). Among the individual components of MetS,

BMI (HR, 1.12; 95% CI, 1.01-1.25), blood pressure (HR, 1.25; 95% CI, 1.05-1.50) and triglycerides (HR, 1.39; 95% CI, 1.15-1.69) were associated with increased risk of cervical cancer. In the models additionally adjusted for BMI and all metabolic factors simultaneously, the associations persisted for blood pressure and triglycerides.

Analyses stratified by histological type revealed somewhat stronger associations of triglycerides with SCC (HR, 1.48; 95%CI, 1.20-1.83) than for ADC (HR, 0.92; 95%CI, 0.54-1.56) (table 4), blood pressure (SCC HR, 1.28; 95%CI, 1.05-1.57 vs. ADC HR, 1.09, 95%CI, 0.65-1.83) and MetS score, respectively (SCC HR, 1.28; 95%CI, 1.08-1.51 vs. ADC HR, 0.98, 95%CI, 0.63-1.52).

Stratification by attained age (<50, 50-70; $\geq$ 70 years, table 5) showed associations between cholesterol (HR, 1.34; 95% CI, 1.00-1.81) and triglycerides (HR 1.49, 95% CI, 1.03-2.16) and cervical cancer among women aged 50-70 years. Among older women aged 70 years or more, glucose (HR 1.87, 95% CI, 1.13-3.11), triglycerides concentrations (HR 1.54, 95% CI, 1.09-2.19), and MetS score (HR, 1.34: 95%CI, 1.03-1.74) were associated with increased cervical cancer risk.

Discussion

The MetS score was associated with increased risk of cervical cancer in this large, prospective study. Several of the individual MetS components including BMI, blood pressure and triglycerides were significantly associated with increased cervical cancer risk. Triglycerides, blood pressure and the MetS score were stronger confined to SCC than to ADC. Among women with attained age 50 years and older metabolic factors were associated with cervical cancer risk.

In our study, BMI by z-score was positively associated with risk of cervical cancer and the test for linearity was of borderline statistical significance (p for trend 0.06). Previous research

1 showed mixed results; some studies have reported an increased risk (10)(16)(29), others
2 decreased risk (19), and some authors found no association (13). The strength of the
3 association in previous studies may depend on the proportion of ADC. In studies where
4 results by histological subtype were reported, a stronger association was observed between
5 BMI and ADC than for SCC (10). We found no statistically significant association between
6 BMI and cervical cancer subtypes. Wee et al. found no associations between obesity or with
7 sexual behavior related risk factors and HPV prevalence (30). A possible biological link could
8 be insulin and insulin like growth factors, which in-vitro stimulated invasiveness and
9 proliferation of cervical cancer cells (31) and were associated with HPV infection (32), and
10 cervical cancer in clinical studies (33). In a small nested case-control study, higher resistin
11 and sFas levels were found among women with persistent HPV infection suggesting that
12 obesity is associated with the persistence of HPV infection (22). There is evidence from the
13 mouse model that estrogen contributes to the development of cervical cancer by synergy with
14 the HPV oncogene (21).

15
16 Our observation that high triglycerides concentrations were associated with increased risk of
17 cervical cancer is consistent with previous research (19). In our analyses, the adjustment for
18 other metabolic factors actually strengthened the association between triglycerides and
19 cervical cancer, indicating that the relationship is independent of other metabolic factors. Our
20 observation of a stronger association of triglycerides with SCC than ADC is consistent with
21 the literature suggesting differential age distribution, pathological pathways and HPV
22 genotype attribution and persistence (6)(10)(12)(34) Differences in co-factors were related to
23 smoking which was associated with SCC, but not with ADC (12), and obesity, which was
24 associated with ADC, but not SCC (10). Results from a nested case-control study suggest

1 that persistent HPV infection is associated with increased levels of inflammatory cytokines
2 (35). Further research is necessary to clarify the differential mechanisms.

3 Overall, we found no association of glucose and cholesterol levels with cervical cancer risk.
4 Among older women, however, we observed associations of glucose (age 50-70 years) and
5 cholesterol concentrations $\geq$ 70 years) with cervical cancer risk. Mixed results have been
6 published on the association between manifest diabetes and cervical cancer (36)(37). Jee et al.
7 found an association for diabetes, but blood glucose levels were not statistically significantly
8 associated with the risk of cervical cancer among Korean women (36). Data on cholesterol
9 concentration and cancer risk are sparse. No association with cervical cancer was reported in a
10 prospective cohort study (38). Possible biological mechanisms include glucose-related
11 pathways which induce the formation of reactive oxygen species (ROS) and affect the
12 immune system.

13 In line with our observation between elevated blood pressure and increased cervical cancer
14 risk, Ursin et al. also found increased risk of cervical cancer for systolic blood pressure (18).
15 Histological types did not modify the association in our study while in the literature mixed
16 results have been reported from clinical-based studies (39)(40). It has been hypothesized that
17 hypertension could be linked to malignancies through the renin-angiotensin-system which has
18 been found to stimulate cell-proliferation, angiogenesis and inflammation in experimental
19 studies (41). In case-control studies, higher vascular epithelial growth factor (VEGF) - one of
20 the most important angiogenesis factors - levels were observed in patients with cervical
21 cancer (42),(43) indicating that angiogenesis, which is triggered by hypoxia, is associated
22 with HPV persistence and growth of HPV lesions (44).

23
24 In our study, the MetS score was associated with increased risk of cervical cancer. To the best
25 of our knowledge, our study is the first report of this association. When looking at different

subtypes of cervical cancer, the association was stronger for SCC than for ADC mainly due to the contribution of triglycerides. Our observation that among older women the MetS score was statistically significantly associated with cervical cancer risk is consistent with reports from cases-control studies on associations between increased adipokines and inflammatory markers in older women with persistent HPV infection (22)(35). Other mechanisms are related to estrogen and angiogenesis (21)(44).

Strengths and limitations

Major strengths of our study are its prospective design and large size, which minimizes selection, recall, and reverse causation bias. In all sub-cohorts, standardized information on the measured exposure factors was derived from population-based surveys, and follow-up for cancer occurrence among cohort members was ascertained through linkages with nation-wide registers in Austria, Norway and Sweden (45)(46)(47). We applied models using quintiles and z-scores of metabolic factors to assess the association between MetS and risk of cervical cancer accounting for measurement error and fluctuation of exposure variables over time correcting the observed risk estimates by the RDR and regression calibration method. Both methods generated stronger associations between the individual and combined metabolic factors and cervical cancer risk, indicating that the true association could be underestimated. To account for differences in the measurement of metabolic factors, cohort-specific cut-off points were used in the analyses. For all cases information we had information on histology.

Limitations of our study concern the lack of detailed information on several potential confounders such as socioeconomic status, sexual behavior, and reproductive factors. Sensitivity analyses for reproductive variables for endometrial cancer in the Norwegian cohort also showed no appreciable changes of the risk estimates (24). Nevertheless, information

about smoking status as risk factor for cervical cancer at baseline was available. Adjustment for smoking in the models did not significantly alter risk estimates. Participation in cervical cancer screening programs is less prevalent in obese women and may have influenced the detection of cervical cancer and its precursor lesions. However, Lacey et al. found in their publication in the US, that adjustment for screening produced similar associations between BMI and cervical cancer (10). In the mutually adjusted models increased risk of cervical cancer for blood pressure and triglycerides was present. In our study, HPV infection is probably of minor interest as confounder, because infection with HPV is virtually present in all cervical cancer cases. However, other risk factors could be necessary for cancer development. Multiple comparisons were performed which needs to be considered for interpretation of the results.

Conclusion

The results of this large prospective study provide the first evidence for an association between cervical cancer and both individual and combined metabolic factors including BMI, blood pressure and triglyceride levels. Different risk patterns of metabolic factors by morphology could be related to difference in the pathogenesis.

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5 ***Conflict of interest***

6 The authors declared no conflicts of interest.

8 ***Author contribution***

9 Gabriele Nagel, Hanno Ulmer, Tanja Stocks, Tone Bjørge, Annekatrin Lukanova, Jonas Manjer,
10 Håkan Jonsson, Pär Stattin were involved in the study conception and design. Tanja Stocks and Pär
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16 Engeland, Göran Hallmans, Håkan Jonsson, and Pär Stattin. All authors were involved in the data
17 analysis and interpretation. Gabriele Nagel and Hanno Ulmer were writing the manuscript, which was
18 finally approved by all authors.

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1 **Table 1:** Description of the study population in the Me-Can project

		Women
Cohort N (%)		
Norway	Trefylker	25,072 (9)
	CONOR	57,687 (20)
	40-y	68,211 (23)
Austria	VHM&PP	86, 671 (30)
Sweden	VIP	40,669 (14)
	MPP	10,524 (4)
Total		288,834
Baseline age (years)		
Mean (SD)		44.1 (12.3)
Categories N (%)		
		-29
		30-39
		40-49
		50-59
		60-69
		70+
Year of birth		
Categories N (%)		-1929
		1930-39
		1940-49
		1950-59
		1960-
Fasting time (hours))		
Categories N (%)		<4
		4-8
		> 8
Smoking status N (%)		
		Never-smoker
		Ex-smoker
		Smoker
		Unknown
BMI (kg/m ²)		
Mean (SD)		24.9 (4.4)
Categories N (%)		< 25.0
		25.0-29.9
		30+
Follow-up (years)		
Mean (SD)		11.3 (6.8)
Categories N (%)		0-9
		10-19
		20+

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NCS=Norwegian Counties Study; CONOR=Cohort of Norway; 40-y=Age 40-programme; VHM&PP=Vorarlberg Heath Monitoring and Prevention Programme; VIP=Västerbotten Intervention Project; MPP=Malmö Preventive Project; SD=standard deviation; BMI=body mass index.

Table 2: Hazard ratios (HRs) with 95% confidence intervals (CI) of cervical cancer by metabolic factors in quintiles

	Quintile	Mean (SD)	Cervical cancer (N=425)	
			N	HR* (95%CI)
BMI (kg/m ²)	1	20.0 (1.2)	82	1.00 (referent)
	2	22.3 (0.8)	74	0.94 (0.66-1.34)
	3	24.1 (0.8)	92	1.24 (0.88-1.73)
	4	26.4 (1.0)	87	1.20 (0.85-1.69)
	5	31.7 (3.6)	90	1.33 (0.94-1.88)
	Ptrend			0.06
Mid Blood pressure (mmHg)	1	84.3 (4.4)	67	1.00 (referent)
	2	93.1 (2.6)	80	1.29 (0.72-2.32)
	3	99.3 (2.5)	92	1.73 (0.97-3.07)
	4	106.6 (3.5)	96	1.60 (0.90-2.85)
	5	122.6 (11.0)	90	1.73 (0.94-3.18)
	Ptrend			0.08
Glucose (mmol/L)	1	4.1 (0.5)	84	1.00 (referent)
	2	4.6 (0.3)	76	0.84 (0.27-2.66)
	3	5.0 (0.3)	92	0.90 (0.30-2.68)
	4	5.3 (0.3)	91	1.51 (0.50-4.53)
	5	6.5 (1.6)	80	0.62 (0.20-1.96)
	Ptrend			0.67
Cholesterol (mmol/L)	1	4.2 (0.4)	80	1.00 (referent)
	2	4.9 (0.3)	87	1.15 (0.72-1.82)
	3	5.4 (0.3)	78	0.95 (0.59-1.54)
	4	6.1 (0.3)	86	1.10 (0.68-1.78)
	5	7.3 (0.9)	92	1.20 (0.74-1.95)
	Ptrend			0.24
Triglycerides (mmol/L)	1	0.6 (0.1)	53	1.00 (referent)
	2	0.9 (0.1)	84	1.78 (0.89-3.53)
	3	1.1 (1.1)	90	2.09 (1.06-4.12)
	4	1.5 (0.2)	83	1.75 (0.88-3.49)
	5	2.5 (1.1)	106	2.80 (1.44-5.46)
	Ptrend			0.06

*Stratified by center, sex and year of birth (categories), and adjusted for age at recruitment (years), smoking status (never-, ex-, current-smoker, unknown), and corrected for measurement error by RDR

Table 3: Hazard ratios (HRs) with 95% confidence intervals (CI) of cervical cancer for z-scores of individual and combined metabolic factors

	Cervical cancer (N=425)					
	HR*	(95%CI)	HR**	(95%CI)	HR***	(95%CI)
BMI	1.12	(1.01-1.25)	-		1.01	(0.87-1.16)
Mid blood pressure	1.25	(1.05-1.50)	1.20	(0.99-1.45)	1.27	(1.04-1.56)
Glucose#	0.95	(0.66-1.37)	0.90	(0.62-1.31)	0.75	(0.50-1.11)
Cholesterol	1.07	(0.92-1.25)	1.05	(0.90-1.23)	0.92	(0.77-1.09)
Triglycerides#	1.39	(1.15-1.69)	1.35	(1.10-1.65)	1.44	(1.34-1.70)
MetS-Score	1.26	(1.09-1.47)	-		-	

*Stratified by center and year of birth (categories), adjusted for age at recruitment (years), smoking status (never-, ex-, current-smoker, unknown), and corrected for measurement error by RDR

**Stratified by center and year of birth (categories), adjusted for age at recruitment (years), smoking status (never-, ex-, current-smoker, unknown), BMI and corrected for measurement error by RDR

***Stratified by center and year of birth (categories), adjusted for age at recruitment (years), smoking status (never-, ex-, current-smoker, unknown), BMI, blood pressure, total cholesterol, and triglyceride and corrected for measurement error by RC

Normal logarithm transformed measures

Table 4: Hazard ratios (HRs) with 95% confidence intervals (CI) of cervical cancer for z-scores of individual and combined metabolic factors by morphology[‡]

	SCC (N=337)		ADC (N=59)	
	HR*	(95%CI)	HR*	(95%CI)
BMI	1.09	(0.97-1.23)	1.19	(0.90-1.57)
Mid blood pressure	1.28	(1.05-1.57)	1.09	(0.65-1.83)
Glucose#	0.87	(0.58-1.32)	0.84	(0.31-2.33)
Cholesterol	1.06	(0.90-1.26)	1.00	(0.66-1.53)
Triglycerides#	1.48	(1.20-1.83)	0.92	(0.54-1.56)
MetS-Score	1.28	(1.08-1.51)	0.98	(0.63-1.52)

[‡] SCC squamous cell carcinoma, ADC adeno carcinoma of the uterine cervix, 29 cases other morphology

*Stratified by center and year of birth (categories), and adjusted for age at recruitment (years), smoking status (never-, ex-, current-smoker, unknown), and corrected for measurement error by RDR

Normal logarithm transformed measures

Table 5: Hazard ratios (HRs) with 95% confidence intervals (CI) of cervical cancer for z-scores of individual and combined metabolic factors by attained age

	Attained age <50 years (N=95)		Attained age 50-70 years (N=209)		Attained age ≥70 years (N=121)	
	HR*	(95%CI)	HR*	(95%CI)	HR*	(95%CI)
BMI	1.04	(0.83-1.31)	1.11	0.90-1.36	0.97	0.79-1.19
Mid blood pressure	1.13	(0.74-1.74)	1.03	0.69-1.54	1.28	0.95-1.72
Glucose#	0.71	(0.31-1.63)	0.48	0.23-1.02	1.87	1.13-3.11
Cholesterol	1.33	(0.96-1.84)	1.34	1.00-1.81	0.97	0.74-1.27
Triglycerides#	1.42	(0.95-2.13)	1.49	1.03-2.16	1.54	1.09-2.19
MetS-Score	1.23	(0.88-1.71)	1.20	0.88-1.62	1.34	1.03-1.74

*Stratified by center and year of birth (categories), and adjusted for age at recruitment (years), smoking status (never-, ex-, current-smoker, unknown), and corrected for measurement error by RDR

Normal logarithm transformed measures