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Metabolic syndrome and cancer risk

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ABSTRACT

Objective: The purpose of this population-based study is to explore for the first time the link between metabolic syndrome and cancer risk using information from the health information system of the Cancer Registry.

Methods: Referring to all pharmaceutical prescriptions between 1 January 1999 and 31 December 2005, coded with the *Anatomical Therapeutic Chemical* classification, all subjects aged 40 and over resident in Milan, which were simultaneously prescribed with antihypertensive, hypolypemic and hypoglycaemic drugs, were considered affected by metabolic syndrome. New cancer cases among cohort subjects were identified trough the local Cancer Registry and standardised incidence ratios (and corresponding 95% exact confidence intervals) were computed.

Results: Overall 16,677 subjects were identified corresponding to 45,828 person-years; among them 823 incidents cancers occurred. Significantly increased risks for pancreatic cancer in males - SIR 178 (114–266) - and colorectal cancer in females - SIR 133 (101–170) - were observed. Non-significantly increased risks were also observed in women for liver, gallbladder and biliary tract, breast and endometrial cancers.

Conclusions: Our study suggests that the risk for several cancers increases in subjects affected by metabolic syndrome. The pharmacological control of the syndrome seems to be inadequate for reducing cancer risk, even though both a high competitive mortality effect and short duration of follow up have to be considered.

1. Introduction

Metabolic syndrome is defined as a combination of cardiovascular risk factors which include increased body mass index (or waist circumference), blood pressure, glycemia, and serum triglycerides, as well as a decrease in high-density lipoprotein cholesterol.[1–4]

Interestingly, most components of metabolic syndrome have each been linked in some way to the development of cancer. Hypertension may increase cancer risk by blocking and subsequently modifying apoptosis, thereby affecting cell turnover.[5,6] Several studies showed a positive relationship between diabetes and pancreatic and liver cancers caused by the insulin excess which promotes the development of cancer cells in the liver and pancreas.[7–11] Obesity is a major risk factor for cancer; prospective studies indicate that overweight and obesity account for 14% of all cancer deaths in men and 20% in women.[12] Obesity is implicated in aetiology and progression of cancer at multiple cancer sites by means of signalling pathways that regulate key functions, including cancer cell proliferation, apoptosis, metastasis, and angiogenesis.[13–15]

Yet, bearing such evidence, based on the related components of metabolic syndrome, epidemiological studies linking metabolic syndrome to cancer are scarce.[16–20]

The purpose of this study is to explore the relationship between metabolic syndrome and cancer risk. Referring to the

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health information system and to the Cancer Registry of Milan, subjects simultaneously treated with hypoglycaemic, anti-hypertensive and hypolipemics drugs were assigned to a pharmacological diagnosis of metabolic syndrome. Specifically, under the hypothesis that those subjects have a higher risk of developing cancer, we systematically analysed their risk cancer differences with the general population across all cancer sites.

2. Materials and methods

This study was carried out using Milan's Health Authority information system, which covers the largest metropolitan population in the North of Italy (about 1,300,000 inhabitants).

All drugs prescribed to the resident population of Milan are listed in the *Pharmaceutical Prescriptions Archive* and coded with the *Anatomical Therapeutic Chemical* (ATC) classification. All pharmaceutical prescriptions in the time period between 1 January 1999 and 31 December 2005 ($N = 42{,}626{,}531$) were retrieved to identify subjects resident who received prescriptions for antihypertensive (ATC codes: C02–C03, C07–C09), hypoglycaemic (ATC code: A10) and hypolypemic (ATC code: C10) drugs. Subjects aged 40 and over, who chronically received such a combined treatment during the study period were considered affected by hypertension, diabetes and dislipidemia at the same time, a condition which induced a *pharmacologically based* diagnosis of metabolic syndrome and, consequently, inclusion in the study cohort.

The main outcome of the study (i.e. the subsequent diagnosis of an incident invasive cancer) was ascertained through the local Cancer Registry. Topography was coded according to International Classification of Diseases-10th Revision (ICD-X). Vital status was regulated through the Census Office of Milan, and the cause of death, coded according to International Classification of Diseases-9th Revision (ICD-IX), was provided by the local Mortality Registry.

The index date for time event calculation was defined as the date when each subject started the pharmacological treatment for the last component of metabolic syndrome (antihypertensive, hypoglycaemic and hypolypemic). Cancer events were defined as case incident after the index date: all subjects with cancer occurrence before index date were excluded from the analysis.

The number of person-years at risk contributed by each patient was computed by subtraction of the index date from one of following: date of the first malignant cancer diagnosis, date of death, date of migration, or the last date of follow up (December 31, 2005), whichever came first.

The excess risk of cancer was assessed by the comparison of observed and expected number of cancer cases. The expected number of site specific cancer cases in the cohort were computed multiplying the person-years by the corresponding age-specific cancer incidence rates in the 1999–2002 period estimated by the local Cancer Registry. Standardised incidence ratios (SIRs) were computed as the ratio between observed and expected numbers for each cancer site; the corresponding 95% exact confidence intervals were computed under the assumption of a Poisson distribution of the observed cases. Similar methodology was adopted for the mortality analyses to compute the standardised mortality ratios (SMRs) and the corresponding 95% confidence intervals.

3. Results

A total of 16,677 subjects exposed simultaneously to antihypertensive, hypoglycaemic and hypolypemic treatments were identified and enrolled in the study.

Case follow-up lasted up to 8-years, with an average follow up period of 2.7 years, and a total of 45,828 person-years. During the study period 823 incidents cancers were identified. Table 1 shows the absolute and the expected frequencies of new occurrences by site as classified by ICD-X.

The expected number of invasive cancers, derived from Cancer Registry based incidence rates, were 492 for males (SIR 103; 95% CI 95–113) and 302 for females (SIR 104; 95% CI 93–116).

Significant increased risks were observed for pancreatic cancer in males (SIR 178; 95% CI 114–266); females had a similar but not significant risk increase (SIR 145; 95% CI 87–226). Colorectal cancer risk reached statistical significance in females only (SIR 132; 95% CI 101–170) with a notable increase for rectal cancer subsite (SIR 180; 95% CI 112–276).

Non-significant increased risks were observed for the following cancer sites: liver cancer (SIR 141; 95% CI 97–198) in males and colon (SIR 116; 95% CI 83–158), gallbladder and biliary tract (SIR 159; 95% CI 73–302), breast (SIR 117; 95% CI 95–143) and endometrial cancers (SIR 156; 95% CI 95–241) for females.

Two-fold risk increase was present for thyroid and Hodgkin lymphoma in males and for salivary glands in females; but considering the small number of cases, confidence intervals were very large. Tobacco related cancer (larynx and lung) showed a modest increase in males (SIR 107; 95% CI 87–130) and a most relevant decrease in female (SIR 66; 95% CI 39–104).

Mortality follow up was completed by January 1, 2006: 1746 deaths occurred in the cohort (989 males); for all of which the underlying cause of death was available. A total of 867 deaths were caused by cardiovascular diseases: SMRs were 195 for males (95% CI 178–213) and 168 for females (95% CI 151–186). Mortality for all invasive cancers accounted for 345 deaths: SMRs were 73 for males (95% CI 64–84) and 81 for females (95% CI 68–95), respectively.

4. Discussion

Adopting a *pharmacologically based* definition of metabolic syndrome, our study identified a positive association of this nosological entity with several cancer sites. In particular, the strongest associations were found with pancreatic cancer in men and colorectal cancer in women, but remarkable risk increases were identified for several sites (liver cancer in males and biliary tract and corpus uteri in females).

Our study has several important strengths: it is population based; results are based on a large cohort; incident cancer cases are detected by a cancer registry which assures completeness and quality of relevant information; the recruitment of metabolic syndrome cases did not deserve expensive and long lasting blood determinations.

Table 1 – Standardised Incidence Ratio (SIR) and corresponding 95% confidence intervals (95% CI) based on the observed (O) and expected (E) frequencies of incident cancers

Site	ICD-X topogrpahy	Males			Females			Total		
		O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)
Upper digestive tract	C01–C06, C09–C11	8	7.7	104 (45–205)	3	3.1	96 (20–281)	11	11	102 (51–182)
Salivary glands	C07–08	0	1.1	0 (0.00–2.7)	1	0.54	185 (4.7–1032)	1	1.7	60 (1.5–334)
Oesophagus	C15	4	4.6	86 (24–221)	1	1.6	63 (1.6–350)	5	6.2	80 (26–188)
Stomach	C16	25	22	115 (75–170)	4	14	28 (7.8–73)	29	36	81 (54–117)
Colorectal cancer	C18–C21	60	66	91 (70–117)	61	46	132 (101–170)	121	112	108 (90–129)
Colon	C18	44	48	92 (67–123)	40	34	116 (83–158)	84	82	102 (81–126)
Rectosigmoid junction and rectum	C19–21	16	18	90 (51–146)	21	12	180 (112–276)	37	29	126 (88–173)
Liver and intrahepatic bile ducts	C22	33	23	141 (97–198)	5	8.8	57 (18–132)	38	32	118 (84–162)
Gallbladder and biliary tract	C23–24	6	5.2	116 (42–252)	9	5.7	159 (73–302)	15	11	138 (77–228)
Pancreas	C25	24	13	178 (114–266)	19	13	145 (87–226)	43	27	162 (117–218)
Larynx	C32	13	12	109 (58–186)	1	1.1	89 (2.2–493)	14	13	107 (58–179)
Bronchus and lung	C34	100	94	107 (87–130)	18	27	66 (39–104)	118	121	98 (81–117)
Melanoma of skin	C43	7	9.3	75 (30–155)	2	4.9	41 (4.9–147)	9	14	63 (29–120)
Breast	C50	0	1.8	0 (0.00–1.7)	99	84	117 (95–143)	99	86	115 (93–140)
Cervix uteri	C53	–	–	–	2	3.4	59 (7.2–214)	2	3.4	59 (7.2–214)
Corpus uteri	C54	–	–	–	20	13	156 (95–241)	20	13	156 (95–241)
Ovary	C56	–	–	–	10	9.5	106 (51–194)	10	9.5	106 (51–194)
Prostate	C61	94	101	93 (75–114)	–	–	–	94	101	93 (75–114)
Kidney and urinary tract	C64–66, C68	14	18	76 (42–128)	10	7.6	132 (63–243)	24	26	92 (59–138)
Bladder	C67	54	49	109 (82–143)	10	11	91 (44–168)	64	60	106 (82–136)
Brain and nervous system	C70–72	6	5.8	104 (38–226)	3	3.6	84 (17–244)	9	9.4	96 (44–182)
Thyroid	C73	4	1.9	207 (56–531)	3	3.4	90 (18–262)	7	5.3	133 (53–273)
Hodgkin s disease	C81	2	0.89	225 (27–812)	0	0.56	0 (0.00–5.3)	2	1.5	138 (17–498)
Non-Hodgkin s lymphoma	C82–85. C96	14	16	87 (48–147)	13	11	115 (61–196)	27	27	99 (65–144)
Multiple myeloma	C88–90	4	5.7	70 (19–179)	2	4.5	45 (5.4–161)	6	10	59 (22–128)
Leukaemia	C91–C95	10	10	97 (47–179)	4	6.9	58 (16–149)	14	17	81 (45–137)
Other sites not listed (but C44)		21	14	154 (95–235)	10	9.3	107 (52–198)	31	23	135 (92–191)
Unknown site		5	8.9	56 (18–131)	5	8.0	62 (20–145)	10	17	59 (28–109)
All site, but skin (C44)		508	492	103 (95–113)	315	302	104 (93–116)	823	794	104 (93–116)

However, the study presents several limitations; the most important of them coincide with the last mentioned strength point. The metabolic syndrome is usually based on: a) blood determinations in a standardised laboratory of several analytes (total cholesterol, total triglycerides, high-density lipoprotein, low-density lipoprotein, and serum glucose); b) blood pressure measurements and c) anthropometric indices retrieved through standard protocols.[1–3] This complex and costly pathway to the detection of patients affected by metabolic syndrome is the most likely cause for the limited number of epidemiological studies on metabolic syndrome and cancer (mainly prostate and colorectal cancer).[16–20] Most of them are based on a small number of subjects and therefore do not have sufficient power to assess moderate-sized effects.On the other hand, those studies rely on a single point in time measurement of specific analytes to detect patients of metabolic syndrome; this may introduce misclassification and, even more so, it is not consistent with the natural history of cancer.

Potential selection bias is another limit of our study. Metabolic syndrome cases which require chronic pharmacological treatment identify a population at very high risk and this may undermine the conclusions of our study.

A recent research based on 11 prospective European cohorts reported a prevalence of metabolic syndrome of 15.7% in men and 14.2% in women [21]; however, prevalence reported in the United States based on the NHANES III study was higher, reaching 23%.[22]

Even though the 16,677 subjects of our study, identified through drug prescriptions only, represent a very large sample of metabolic syndrome patients, they are only 2% of the population aged 40 and over (with small difference between genders), indirectly confirming the selection introduced by our recruitment methodology.

Pharmacologically defined metabolic syndrome seems to be related to an excess risk of cancer in selected sites; however, due to the large number of comparisons, chance associations cannot be ruled out and the postulated relationship emerged from this descriptive analysis should be cautiously considered. Nonetheless, most of the detected associations are plausible, as they are in sound agreement with those re-

ported from aetiologic studies on single components of metabolic syndrome and cancer risk.[7–22]

Mortality analysis showed a 2-fold increase of cardiovascular deaths and a 20% decrease in cancer mortality. But, even in the presence of very high competitive mortality in cardiovascular disease and a limited follow up (the mean was 2.7 years), a significant association emerged with pancreatic cancer. Wideroff and colleagues[7] found a 2-fold increase in pancreatic cancer in both sexes combined.

Significant association with colorectal cancer was found only for females. Ahmed and colleagues[20] reported that metabolic syndrome represents a modest risk factor for colorectal cancer in men (with a dose-response effect according to the number of components contributing to the metabolic syndrome definition) but not in women. In a recent study, Stürmer and colleagues[17] found that overweight and diabetes are risk factors for colorectal cancer, whereas elevated blood pressure and hypercholesterolaemia are not.

Our study found a 41% risk increase of liver cancer in men and 59% of biliary tract cancer in women. Several authors[7,9] reported a 3–4-fold increase of liver cancer in diabetic subjects with higher risk in men. Devila and colleagues,[10] using a population based study, found that diabetes was associated with a 2–3-fold increase in liver cancer, regardless of the presence of HCV, HBV, alcoholic liver disease, or non-specific cirrhosis.

Several studies found a positive association between diabetes and endometrial cancer, but for most of them the association may be confounded by obesity.[23–26] Most obese individuals are insulin-resistant and since insulin resistance decreases sensitivity to insulin, more insulin is seceted in the attempt to maintain glucose homeostasis: the overall result is a compensatory hyperinsulinaemia and elevated serum insulin concentrations which increase the bioavailability of insulin-like growth factor-I (IGF-I) which plays an important role in cancer cell proliferation, adhesion, migration and apoptosis.[27]

In our study, positive association for endometrial and breast cancer was found: Furberg and colleagues[26] found that hypertension, hyperglycemia and being overweight are significant risk markers for endometrial cancer, especially among the heaviest women with low HDL cholesterol, as part of metabolic syndrome, and associated with increased postmenopausal breast cancer risk.

In our sample, a non-significant inverse association with prostate cancer was found. Recently, the ARIC Study[18] published an inverse association between metabolic syndrome and prostate cancer, hypothesising that this finding reflects a decrease in bioavailability of testosterone due to an increase in circulating blood lipids with a corresponding increase in binding forms.

In conclusion, our study adds information to the extensive body of knowledge existing on cancer association with metabolic syndrome using a '*low cost*' study design based on a data-warehouse which combines the information system of drug prescriptions and the local cancer registry. Furthermore, cancer risk increase was even found in the presence of increased mortality for cardiovascular disease (competitive effect) and pharmacological control of cardiovascular risk (exposure reduction), confirming that metabolic syndrome or its components are associated to cancer and that their modification does not reduce short-term cancer risk. The study design based on the access to health databases provides challenging opportunities for epidemiologists to explore new hypotheses through the follow up of large cohorts.

Conflict of interest statement

None declared.

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