Adrenal incidentalomas are tied to increased risk of diabetes: findings from a prospective study.

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Declaration of Interest:

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

ABSTRACT

Context

The frequency of adrenal incidentalomas and their association with comorbid conditions have been assessed mostly in retrospective studies that may be prone to ascertainment bias.

Objective

To evaluate the frequency of adrenal incidentalomas and their associated comorbid conditions.

Design

Prospective cohort study.

Setting

Radiology Department at a public hospital.

Partecipants

Unselected outpatients who underwent an abdominal CT from January 2017 to June 2018. Patients with known or suspected adrenal disease or malignancy were excluded.

Exposure

All abdominal CT scans were evaluated by an experienced radiologist. Hormonal work-up including a 1-mg dexamethasone suppression test was done in patients bearing adrenal incidentalomas.

Main outcome and Measure

Frequency of adrenal incidentalomas in abdominal CT of unselected patients; frequency of comorbid conditions, and hormonal work-up in patients bearing adrenal incidentalomas.

Results

We recruited 601 patients and in 7.3% of them an adrenal tumor was found serendipitously. The patients bearing an adrenal incidentaloma had higher BMI (p=0.009) and waist (p=0.007) and were more frequently diabetic (p=0.0038). At multivariate regression analysis, diabetes was significantly associated with the presence of adrenal incidentalomas (p=0.003). Autonomous cortisol secretion was observed in 50% of patients who did not suppress cortisol <50 nmol/L after 1 mg dexamethasone.

Conclusions

The frequency of adrenal incidentalomas is higher than previously reported. Moreover, adrenal incidentalomas are tied to increased risk of type 2 diabetes. This finding is free from ascertainment bias because patients with adrenal incidentalomas were drawn from a prospective cohort with the same risk of diabetes than the background population.

INTRODUCTION

Adrenal tumors are among the most common neoplasms in humans, and the widespread use of high-resolution cross-sectional imaging in medical practice has increased the frequency of their detection, which in most cases occurs serendipitously as adrenal incidentalomas. These tumors are unexpectedly found in patients who undergo abdominal scanning for reasons unrelated to any previously suspected adrenal disease.

The frequency of adrenal incidentalomas in CT series assessed in the 1980s and '90s ranged from 0.35 to 1.9% (1-6). In 2006, we reported a frequency of 4.4% in a sample of 520 subjects at risk of lung cancer who volunteered for CT screening (7), and more recent studies have confirmed a frequency of about 5% (8). This greater frequency of detection is most likely due to the improved resolution of modern imaging.

Most adrenal incidentalomas are benign cortical adenomas that may have secretory activity, although patients do not present the classic stigmata of adrenal steroid excess. In 20-30% of adrenal incidentalomas, an autonomous cortisol secretion is found that may have clinical consequences (9-12). To standardize and simplify heterogeneous clinical practice, the European Society of Endocrinology and the European Network for the Study of Adrenal Tumors (ESE/ENSAT) guidelines recommended a 1 mg overnight dexamethasone suppression test (DST) to exclude cortisol excess (10). Cortisol levels following DST < 50 nmol/L (1.8 µg/dL) exclude autonomous cortisol secretion, while levels > 138 nmol/L (5.0 µg/dL) should be considered as evidence of autonomous cortisol secretion, and levels between the two cutoff points as evidence of possible autonomous cortisol secretion (10).

Autonomous cortisol secretion has been defined as subclinical Cushing's syndrome or subclinical hypercortisolism, and represents the lower end of the Cushing's syndrome spectrum. An increasing body of evidence suggests that is associated with metabolic and cardiovascular diseases that may eventually result in excess mortality (13-19).

It is biologically plausible that chronic exposure to low-grade cortisol excess resulting from autonomous adrenal secretion has clinical consequences, but previous studies are mostly retrospective and cannot definitively establish a cause and effect relationship. An inherent bias of these studies is that diseased individuals are more likely to undergo imaging examinations than healthy ones, and therefore the association between adrenal incidentalomas and diseases such as diabetes, hypertension, and metabolic syndrome may to some extent be explained by an ascertainment bias (20).

Thus, we were prompted to conduct a prospective assessment of patients undergoing abdominal CT examinations at a single radiologic unit, with the following aims: i) to evaluate the frequency of adrenal incidentalomas in an unselected population consecutively recruited; ii) to evaluate whether patients bearing adrenal incidentalomas present more comorbid conditions and increased cardiovascular risk than patients without adrenal tumors; and iii) to evaluate the presence of autonomous cortisol secretion, as defined by the ESE/ENSAT guidelines (10), and its eventual association with comorbid conditions.

SUBJECTS AND METHODS

We conducted a prospective study at the Radiology Department of the S. Croce e Carle Hospital in Cuneo, Italy, between January 2017 and June 2018, on a consecutive series of outpatients who were required to undergo abdominal CT examinations as part of their management. One endocrinologist (EC) attended the Radiology Department one day per week to recruit potentially eligible participants, explaining the purpose of the study and interviewing patients. Those with any history of adrenal disease, malignancy, major psychiatric disorder, or who were on previous or current steroid treatment, or any drug (including estrogens) known to interfere with steroid hormone secretion and metabolism, were considered as non-eligible. We also excluded patients who underwent CT for oncological screening or suspected cancer. All of the study procedures were approved by our institutional research and ethics review board and all the patients included in the study provided written informed consent.

The height (cm) and weight (kg) of the patients, in light clothing and without shoes, were measured using the same device. Body mass index [BMI (kg/m^2)] was then calculated and a BMI of >30 kg/m^2 was considered as evidence of obesity. Participants were considered to have abdominal obesity if their waists were >102 cm for males or >85 cm for females. Blood pressure (mm Hg) was recorded twice using a mercury manometer in a sitting position after the patient rested for more than 15 minutes, and the average value was calculated. Hypertension was defined as blood pressure >140/90 mm Hg, or current use of antihypertensive medications. Diabetes mellitus was defined when the patient reported fasting glycemia ≥ 7 mmol/L, glycemia at 2 h during the oral glucose tolerance test ≥ 11.1 mmol/L, glycated hemoglobin level (HbA1c) ≥6.5%, a previous diagnosis of diabetes, or current use of anti-diabetic medications. Dyslipidemia was defined by the current use of cholesterol-lowering medications. Any history of cerebrovascular or cardiovascular disease (TIA, stroke, angina pectoris, myocardial infarction, or revascularization procedures) was carefully established. Current smoking was defined as smoking at least 1 cigarette per day in the past 12 months. We classified women as menopausal if their final menstrual period had occurred more than 12 months before.

All abdominal CT scans were evaluated by an experienced radiologist (MG), who reported the presence and number of adrenal tumors and their characteristics [largest size, margins, mass texture and attenuation index, which are described as Hounsfield Units (HU)]. The minimal size of adrenal lesions to be considered as incidentalomas was ≥10 mm. In case of multiple lesions, the characteristics of the largest lesion were used for analysis. CT examinations were performed with a Brilliance 64 scan (Philips, Eindhoven, The Netherlands). The technical parameters of CT acquisition were adjusted according to the clinical request for the CT scan and to the patient body size. The section thickness was 2.5 mm. A helicoidal scan was carried out with 120 kV, 300 mAs, a rotation time of 0.42 s, and a pitch of 1.375. In the event of finding an adrenal mass, a multiplanar reconstruction of the whole tumoral area in the sagittal, coronal, and oblique planes was done, with a thickness and reconstruction interval of 1 mm, instead of 2.5 mm used in the initial CT evaluation. Radiologists reported the maximal density observed in the region of interest.

The patients bearing adrenal incidentalomas underwent further work-up, including routine biochemical assessment, plasma fractionated metanephrines, ACTH, DHEA-S, and a 1 mg overnight dexamethasone suppression test (DST). Plasma Renin Activity and aldosterone were evaluated in hypertensive patients. Blood samples were obtained in the morning after overnight fasting. Hormonal determinations were conducted in a single lab with routinely available reagents. In particular, serum cortisol concentrations were measured using a chemiluminescence immunoassay (CLIA, Siemens), with an inter- and intra-assay variation coefficient of 3.7-4.2% and 4.4-6.0%, respectively. DHEAS concentrations were measured using a chemiluminescence immunoassay (CLIA, Siemens), with an inter- and intra-assay variation coefficient of 4.0-5.6% and 1.6-2.5%, respectively. ACTH concentrations were measured using a chemiluminescence immunoassay (CLIA, Diasorin), with an inter- and intra-assay variation coefficient of 2.6-5.5% and 2.7-4.3%, respectively.

Statistical analysis

Variables were preliminarily tested for normal distribution with the Shapiro-Wilks W test and data were expressed as mean ± SD, or median and interquartile range (IQR), as appropriate. Continuous variables were compared by the Student's t-test assuming equal or non-equal variance with the Leneve test. Categorical variables were compared by the Chi-square test or Fisher's exact tests. Two separate sets of linear regressions were conducted, and the presence of an adrenal incidentaloma was set as the dependent variable. The first set was univariate, and the second included all the variables whose β-coefficient was significant in the univariate analysis. In the case of multiple independent variables, a multicollinearity test was performed. Variables were rejected from the analysis if there was a variance inflation factor greater than two. All statistical analyses were performed using SPSS (IBM SPSS Statistics, Version 21). The level of statistical significance was set at $p < 0.05$.

RESULTS

A total of 601 patients were recruited (331 males and 270 females), aged 63.5 ± 14.4 years. They underwent CT imaging for the following reasons: urological evaluation (25.4%); varying abdominal symptoms (25.1%); virtual colonoscopy (18%); alteration in liver function tests (4.3%); alteration in pancreatic enzymes (2.8%); abdominal pain (18%); angiographic studies (16%); hematochezia (6.5%); and other reasons (9%).

The demographic, clinical, and biochemical features of the whole series are summarized in **Table 1**. The demographic characteristics of our cohort are comparable to those of 1332 non-oncologic patients undergoing CT examinations at the same radiology department over a 12-month period (male, 62.2%; age, 67.9 ± 13.2 years). In terms of clinical characteristics, 55.4% of our patients had hypertension, 15.5% had diabetes, 17.3% dyslipidemia and 17% a history of previous CV events. The frequency of diabetes in the study cohort was comparable to that of the general population of the region, which is Piedmont (21,22).

An adrenal tumor was found serendipitously in 44 patients (7.3%). These were 32 males and 12 females aged 65.6 ± 10.3 years. The mass size ranged between 10-50 mm (median 21 mm) and the tumors were bilateral in 29.5% of patients. In a single case that showed indeterminate features, which was 4 cm in size with a density of 30 HU, plasma metanephrine levels were greater than 2 times the upper limit of normality, and histology confirmed a diagnosis of pheochromocytoma. The radiologic re-assessment using a dedicated protocol of the 43 adrenal adenomas led to detection of 11 tumors (25.6%) with a density ranging from 11 HU to 24 HU (Figure 1). In 9 of these patients, a second CT was done after 3 to 12 months, and radiologic characteristics of the tumors remained unchanged. Thirty-two tumors had the radiological features of benign cortical adenoma (density ≤10 HU).

A comparison between patients with adrenal incidentalomas and without is given in **Table 2**. In summary, the patients bearing an adrenal incidentaloma were more frequently males, had higher BMIs ($p = 0.009$) and larger waists ($p = 0.007$), and were more frequently diabetic ($p = 0.0038$) (**Table 2**). The overall distribution of patients with adrenal incidentalomas by age decades was not

fully linear with that of diabetic patients with adrenal incidentalomas (Figure 2), and age of patients bearing adrenal incidentalomas with or without diabetes did not differ significantly (69.9 ± 7.1 years vs. 63.6 ± 11.0 years; p=NS). In the multivariate regression analysis, diabetes was significantly associated with the presence of adrenal incidentalomas (p = 0.003) (**Table 3**). A 1-mg DST was conducted on 40 of the patients, and 20 (50%) did not suppress cortisol < 50 nmol/L, while 4 had post-DST cortisol > 138 nmol/L. A comparison between patients stratified by post-DST cortisol < 50 nmol/L and ≥ 50 nmol/L is provided in **Table 4**. In summary, no significant difference was found in the demographic and clinical characteristics between the two groups, while the size of the dominant nodule was significantly larger in patients with post DST cortisol ≥ 50 nmol/L (p = 0.012). The difference in mass size was not significantly different when considering the sum of sizes in the event of multiple nodules (31.6 ± 16.0 mm vs. 26.2 ± 14.4 mm; p=NS). DHEAS and ACTH concentrations were lower in patients with post DST cortisol ≥ 50 nmol/L; however, levels of statistical significance were not attained.

DISCUSSION

The present study demonstrates that the frequency of adrenal incidentalomas in a prospective series of patients is 7.3%, which is higher than previously reported (**Table 5**)(1-8,23-25). It is important to note that we assessed outpatients without any history of adrenal diseases or malignancy, so we may conclude that this series is unselected, as far as can be assumed for patients under diagnostic evaluation.

The frequency of adrenal incidentalomas identified in published studies is highly variable, as it is dependent on the clinical context, patient characteristics (mainly oncological patients or subjects with known endocrine diseases have been included), and the technology used. The data obtained by first-generation CT scans showed a very low prevalence of about 0.6% (26). In the following decade, the introduction of more advanced CT scans resulted in an increased frequency of about 4%, but different criteria were used and either oncological patients or subjects with a known diagnosis of hypercortisolism were included (7,23,24). More recent studies have shown that adrenal masses can be

found in up to 10% of patients with lung cancer (27). Interestingly, a large study involving all hospitals in Western Sweden reported that the frequency increased from only 0.9% at the first radiological evaluation to 4.5% after a central radiologic revision (23). This suggests the possibility of an underestimation when the evaluation is not carried out by experienced radiologists. The difference was striking, particularly when thoracic CT (extended to the upper abdomen) was considered (23). We found a frequency of bilateral adrenal adenomas of 29.5%, a figure that is higher than previously reported. In the literature, the frequency of bilateral adrenal masses (not only adenomas) ranged from 0% to 25.1% (2,7,8,23-25,28,29). Our study highlights also the importance of a dedicated re-assessment of CT images of any adrenal mass found with a standard radiologic protocol. Interestingly, a previous study employing central revision of CT images reported a frequency of bilateral masses alike the present one (25.1%) (23). In our study, a thickness and reconstruction interval of 1 mm of the whole tumoral area allowed for a more precise assessment of mass density, showing that 25.6% of adrenal adenomas present with unenhanced density between 10 HU and 24 HU (Figure 1). Previous studies reported variable estimates, ranging from 12% to 55% (8,29).

The strength of our study is that the patients were assessed prospectively in a single center, only those referred for abdominal CT were selected, and patients with known or suspected cancer were excluded. The improved methodology in our study (i.e., the revision of all scans by experienced radiologists) could explain the higher frequency than reported in previous studies, with a figure that is close to that of autopsy series. The highest prevalence reported in autopsy series is about 9%, although significant discrepancies of the reported data can occur, depending on the ability to distinguish between hyperplasia and small nodules (26).

The age pattern in our series is similar to those found in previous studies, but the sex distribution differs. We have observed a male predominance, while the bulk of evidence suggests a higher frequency of adrenal incidentalomas in women (5,23). The only findings in agreement with ours are from the recent COAR study (28), which reports a male to female ratio of 1.35. Our assumption is that the specific sex distribution in our study reflects the characteristics of the overall population from

which the series was derived, as a similar sex ratio was found in the population undergoing CT examinations at the Radiology Department where the study was conducted.

A major finding of our study is that adrenal incidentalomas are associated with a higher risk of type 2 diabetes. The patients bearing adrenal incidentalomas have higher BMIs and larger waists, which is consistent with a higher frequency of diabetes. Since the prevalence of either type 2 diabetes or adrenal incidentalomas increases with age, it may be speculated that their association is an effect of aging. However, the correlation between the frequency of adrenal incidentalomas, diabetes and age was not fully linear. Moreover, patients with adrenal incidentalomas were not older than patients without, and age did not differ between patients bearing adrenal incidentalomas with or without diabetes.

The novelty of our findings is that our cohort was unselected; thus, to the best of our knowledge, this is the first unbiased demonstration of a link between adrenal incidentalomas and type 2 diabetes. Discovering adrenal masses in diabetic patients is more likely because they are more extensively studied and followed due to their disease and accompanying comorbidities (20), but this potential limitation does not apply to our study. Our study cohort, from which patients with adrenal incidentalomas were drawn, was composed of outpatients who showed a prevalence of diabetes comparable with the background population of our region (21).

The present data provide strong evidence to support the view that patients with adrenal incidentalomas have a worse metabolic profile, which is associated with increased cardiovascular risk (13-16,18). The observation that diabetes was an independent predictor of the presence of adrenal tumors points to the relationship with insulin resistance, which may be bidirectional, as recently argued by Sydney et al. (30). An adrenal adenoma may be a possible cause of insulin resistance and metabolic syndrome (14), but insulin resistance by itself may facilitate the occurrence of adrenal tumors (31,32).

It is well recognized that type 2 diabetes mellitus represents a risk factor for different cancer types (30), through pathways including the production of TNF-alpha by adipose tissue (33), hyperinsulinemia, and hyperglycemia (34,35).

In terms of the assessment of cortisol secretion, we confirm that approximately half of the patients with adrenal incidentalomas have possible autonomous cortisol secretion, according to the definition in the ESE/ENSAT guidelines (10). Due to the small subgroups, we were not able to separately consider patients with definitive autonomous cortisol secretion, and we compared only two groups stratified by post-DST cortisol of 50 nmol/L, and found no difference in the comorbidity burden between them.

The possibility that even non-functioning adrenal incidentalomas may predict an increased risk of diabetes has been proposed by Lopez et al. (36), who demonstrated in a longitudinal retrospective study how the frequency of incident diabetes found during the follow-up was higher for patients with non-secretory tumors than for those without. More recent studies have suggested that the lack of autonomous cortisol secretion does not exclude an adverse metabolic and cardiovascular profile (13,30,37). A recent meta-analysis assessing morbidity and mortality in patients with adrenal incidentalomas found that diabetes was twice as frequent in patients with autonomous cortisol excess than in patients with non-secretory tumors, although the latter still had a frequency of diabetes higher than the general population (38).

To conclude, we have shown in a contemporary and prospective radiological series that the frequency of unsuspected adrenal tumors (adrenal incidentalomas) is higher than previously reported. In addition, the findings support the association between adrenal incidentalomas and type 2 diabetes. Although this has previously been identified (39), strength of the present study is that our findings are free from ascertainment bias, since patients with adrenal incidentalomas were drawn from a cohort of outpatients showing a risk of diabetes comparable with the background population of our region. The prospective recruitment of our series, and the fact that it was not enriched a priori by diabetic patients, provide strong support to the concept. We acknowledge the limitation that due to the small sample

size of adrenal tumors, the subgroup analysis was not able to establish whether autonomous cortisol secretion has a role in this association. However, the present study provides evidence for a better understanding of whether adrenal incidentalomas are associated with comorbid conditions. Given the frequency of adrenal incidentalomas, which in the present series was even higher than previously thought, the issue is of importance for public health.

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TABLES

Table 1. Baseline features of patients.

N= 601	
Male sex	331 (55.1)
Age, years	63.5 ±14.4
BMI	25.4 ± 4.9
Waist, cm	93.1 ± 13.9
Menopausal status§	208 (77)
Smoking	132 (22)
Hypertension	335 (55.4)
Type 2 Diabetes	93 (15.5)
HbA1c*, %	7.5 ± 1.93
Dyslipidemia	104 (17.3)
History of CV events	102 (17)

Data are expressed as mean ± SD or as absolute value and percentage as appropriate.

§Menopausal status refers to women only.

*HbA1c values refer to 90 diabetic patients.

Abbreviations: BMI = body mass index, HbA1c= glycosylated hemoglobin, CV= cardiovascular.

Table 2. Comparison between patients with adrenal incidentalomas and patients without.

	Patients with Adrenal Incidentalomas (44)	**Patients without Adrenal Incidentalomas (557)**	**p value**
Male sex	32 (72.7)	299 (53.7)	**0.0221**
Age, years	65.6 ± 10.3	63.3 ± 14.7	0.4007
BMI	27.6 ± 6.2	25.6 ± 4.8	**0.009**
Waist, cm	101.2 ± 13.9	92.7 ± 13.9	**0.007**
Hypertension	28 (63.6)	307 (55.1)	0.29
Type 2 Diabetes	14 (31.8)	79 (14.2)	**0.0038**
HbA1c*,%	7.8 ± 2.9	7.2 ± 2.6	0.1446
Dyslipidemia	11 (25)	93 (16.7)	0.2322
History of CV events	7 (16.3)	95 (17.1)	0.9892

Data are expressed as mean ± SD or as absolute value and percentage as appropriate.

*HbA1c values refer to 14 diabetic patients with adrenal incidentalomas and 76 diabetic patients without adrenal incidentalomas.

Abbreviations: BMI = body mass index, HbA1c= glycosylated hemoglobin, CV= cardiovascular.

Table 3. Multivariariate regression analysis of the features associated with the presence of an adrenal incidentaloma.

N= 44		
	Beta value	**P value**
Male sex	0.053	0.216
Smoking	0.082	0.057
BMI	0.016	0.720
Type 2 Diabetes	**0.131**	**0.003**

Table 4: Comparison between patients with cortisol levels after 1 mg dexamethasone suppression < 50 or ≥ 50 nmol/L.

	Patients with cortisol levels after 1 mg dexamethasone suppression < 50 nmol/L. (20)	**Patients with cortisol levels after 1 mg dexamethasone suppression ≥ 50 nmol/L (20)**	**p**
Male sex (n,%)	16 (80)	14 (70)	0.465
Age, years (mean ± SD)	62.6 ± 8.2	67.5 ± 9.5	0.429
BMI (media ± SD)	26.9 ± 5.6	28.5 ± 6.9	0.750
Hypertension (n,%)	9 (45)	15 (75)	0.053
Diabetes (n,%)	6 (30)	7 (35)	0.736
HbA1c, % (mean ± SD)*	7.1 ± 1.8	8.9 ± 3.8	0.114
Dyslipidemia (n,%)	3 (15)	6 (30)	0.256
History of CV events (n,%)	2 (10)	4 (20)	0.376
Size of the dominant nodule (mm)	19.8 ± 7.6	27.4 ± 12.9	**0.012**
ACTH (pmol/L)	3.5 ± 1.5	2.9 ± 1.8	0.114
DHEAS (μmol/L)	1.9 ± 1.1	1.7 ± 1.0	0.739

Data are expressed as mean ± SD or as absolute value and percentage as appropriate.

*HbA1c values refer to diabetic patients only.

Abbreviations: BMI = body mass index, HbA1c= glycosylated haemoglobin, CV= cardiovascular.

Table 5. Frequency of adrenal incidentalomas in CT scan series.

Study	Study period	Patients (n)	Age at diagnosis (years)	Female Sex (%)	Type of CT	Frequency of adrenal incidentalomas (%)	Mass size (mm)	Bilateral mass (%)
Glazer 1982	NA	2200	NA	NA	NA	0.6	NA	NA
Prinz 1982	1981	1423	41 – 73	44.4	Abdominal	0.6	10-40	**0**
Abecassis 1985	1983-1985	1459	NA	NA	NA	1.3	NA	NA
Belldegrun 1986	1976-1983	12000	NA	NA	Abdominal	0.7	NA	NA
Herrera 1991	1985-1989	61054	62	60.2	NA	0.4	25 (10-110)	NA
Caplan 1994	NA	1779	NA	NA	NA	1.90		NA
Song 2008	Jan 2000 - Dec 2003	65231	64 (19 – 100)	NA	Abdominal and thoracic	1.5	20 (4 - 82)	7.8
Hammarstetd 2010	Oct 2002 - Apr 2004	34044	69 (30 – 94)	56.9	Abdominal and thoracic	4.5	25.8 (8–94)	25.1
Bovio 2011	Apr 2001- Dec 2001	520	58 (50 – 79)	26.1	Chest scan	4.4	12-38	13.2
Davenport 2011	Jan 2006 - Dec 2007	3099	68 (45 – 92)	46	Abdominal and thoracic	0.98 abdomen 0.81 thorax	26 ± 12	2.7
Grossman 2016	NA	673	50.93 ± 11.1	NA	Abdominal CT	4.2	NA	11

Present study	Jan 2017 - Jun 2018	601	65.6 ± 10.3	27.3	Abdominal CT	7.3	21 (10-50)	29.5

Abbreviations: NA = Not available.

Legends to figures.

Figure 1. Scatterplot of the density (HU) and size (mm) of adrenal adenomas.

Figure 2. Distribution of patients with adrenal adenomas (white bars) and patients with adrenal adenomas and diabetes (black bars) by age decades.

Figure 1

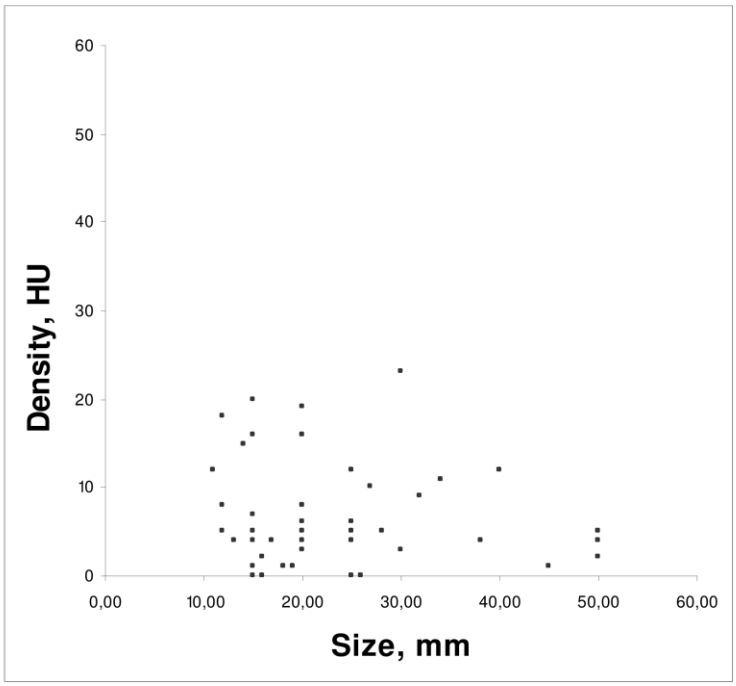

Figure 2