# Changing trends in malignant transformation of hepatocellular adenoma

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## ABSTRACT

**Objective** Hepatocellular adenomas (HCAs) classically develop in women who are taking oral contraceptives and have a risk of malignant transformation into hepatocellular carcinoma (HCC). HCA with malignant transformation is, however, an ill-defined entity thought to be an anecdotic pathway to HCC. The objective of this study was to characterise malignancy occurring within HCA.

**Design, setting and patients** A series of histology proven HCAs managed between 1993 and 2008 in a tertiary hepato-biliary centre (218 patients, 184 women and 34 men) were screened to identify HCA with malignant transformation.

**Main outcome measures** The incidence of HCA with malignant transformation was analysed through the study period and associated conditions were retrieved. They were sub-typed according to their molecular features and the malignant compartment was mapped.

**Results** Areas of HCC within HCA were observed in 23 patients and the risk of malignant transformation was 4% in women and 47% in men. The number of women whose HCA had malignant changes has remained stable during the study period and oral contraception was the only associated condition. The number of men with such transformation has markedly increased since 2000 and the metabolic syndrome has become the most frequent associated condition. Two-thirds of HCAs with malignant transformation were β-catenin activated and one-third displayed cell atypias. Both features were more prevalent in men. The median diameter of HCA with malignancy was 10 cm and only three were 5 cm or less.

**Conclusion** Prevalence of malignancy within HCA is 10 times more frequent in men than in women and management of HCA should primarily be based on gender. Whereas oral contraception is a classical cause of HCA in women but a marginal cause of HCC, the metabolic syndrome appears as an emerging condition associated with malignant transformation of HCA in men, and is the likely predisposing condition for HCC in this setting.

### Significance of this study

**What is already known about this subject?**
- Hepatocellular adenomas (HCAs) are mainly observed in women who are taking oral contraceptives but HCAs are also rarely observed, irrespective of gender, in association wit other conditions (glycogen storage disease, Fanconi's anaemia).
- Malignant changes within HCAs have been described but this condition is ill-defined.

**What are the new findings?**
- Over a 15-year period, the number of HCAs with malignant changes has remained stable in women while it has increased in men. This increase is linked to the metabolic syndrome.
- The proportion of malignant changes in HCAs was 10 times higher in men than in women (4% vs 47%) and the carcinologic pathway appears different in men and women.
- In women who are taking oral contraceptives, malignant changes were not observed within small (<5 cm) HCAs.

**How might it impact on clinical practice in the foreseeable future?**
- Management of HCAs should primarily be tailored to gender.
- The metabolic syndrome is a new risk factor for HCA with malignant transformation in men and HCA is the likely predisposing condition to HCC associated with the metabolic syndrome.

## INTRODUCTION

Hepatocellular adenomas (HCAs) are rare benign tumours, predominantly linked to the use of oral contraceptives (OCs)[1] with a prevalence of 3–4/10[5] in long-term users. This figure was, however, computed in the 1970s on a very limited number of patients[2] and has not been updated for the last generation of OCs. HCAs have also been described in association with rare conditions such as glycogen storage disease[3] or androgen treatments[4] but they account for 5% or less of the cases.[5 6] Up to 45% of the patients in North America[7 8] and 18–25% in European series[5 6] have no identified aetiology.

HCAs have a risk of malignant transformation into hepatocellular carcinoma (HCC). This was first suggested when a well-differentiated HCC partially replacing a benign liver tumour was described in a 21-year-old woman taking OCs.[9] Additional cases have been reported both in pre-existing and previously undiagnosed HCA (reviewed by Larsen *et al*[10] and Micchelli *et al*[11]). These have, nevertheless, remained rare and as OCs also increase the risk of malignant liver tumours[12] it was unclear if HCC arose from the HCA or if both lesions were coincident. Stronger evidence came from the demonstration that HCAs are monoclonal[13] and may contain areas of dysplasia, interpreted as the missing link between the benign

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and malignant components.[14] In addition, some HCAs present a β-catenin-activating mutation[15] which is a common pathway of liver carcinogenesis. β-Catenin-activated HCAs are more likely to harbour unequivocal areas of HCC or to be interpreted as borderline lesions between HCC and HCA.[16]

Malignant transformation has been documented in 0%[17] to 18%[11] of patients with HCA but these figures should be interpreted with caution. They are derived from series of fewer than 50 patients, gathered by specialised hepato-biliary referral centres. In three recent larger cohorts[5 6 8] of similar size (122–128 patients), the incidence ranged from 4 to 8%. Nevertheless, the limited number of patients reported with malignancy within HCA has, so far, prevented an accurate description of this condition. We have therefore updated our previous report on HCA,[6] almost doubling the number of patients ever reported, with the aim of estimating the frequency of HCA with malignant changes, characterising patients with this condition and describing the pathological features of their tumours. Our results provide more accurate guidelines in the management of HCA and gain new insights into the carcinogenesis of HCC associated with a metabolic syndrome.

## PATIENTS AND METHODS

All patients who had undergone complete resection of a tumour with a pathological code of HCA between 1993 and 2008 were retrieved from our hospital database following institutional approval and after having obtained their informed consent. Our policy has been to perform complete surgical resection of HCA in patients with a single tumour and to resect all HCA larger than 3 cm in patients with multiple HCA, irrespective of gender. The search yielded 218 patients (184 women and 34 men) of whom 23 had associated features of HCC thereafter defined as HCA with malignant transformation. These included the presence of atypical areas showing mainly abnormal trabecular pattern with decreased reticulin framework and/or glypican-3 positivity of the hepatocellular proliferation within an HCA. Two additional patients who had undergone surgery elsewhere and whose pathological specimen had been referred for expertise had similar evidence of malignant transformation and were included in the pathological analysis only.

The medical records of the 23 patients operated in our hospital were reviewed to assess their epidemiology, previous and ongoing use of OCs or anabolic steroids, associated conditions, liver function tests, serum α-fetoprotein levels and hepatitis B or C virus (HBV, HCV) serology. As we have recently suspected a link between HCC and previous HCA in patients with a metabolic syndrome[18] we have also searched evidence for this syndrome according to the WHO criteria either retrospectively or by interview.[19]

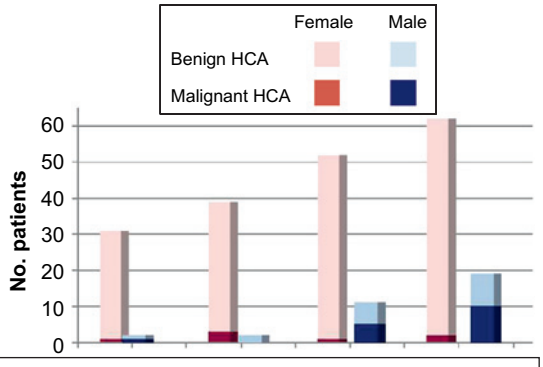
The pathological specimens of the 25 patients (the 23 of our own series and the two referred for expertise) were reviewed to characterise the underlying HCA, map the site of malignant transformation and analyse the adjacent liver parenchyma. One block per square centimetre of HCA was analysed. Sub-typing of HCA according to their patho-molecular classification[15] into telangiectatic/inflammatory, liver fatty acid binding protein (LFABP)-negative steatotic, β-catenin-activated (with or without cell atypias) and unclassified types, was based on both morphological and immunophenotypical features in 23 patients (immunostaining was unavailable in two patients). The following markers were used as previously described[6]: serum amyloid A (SAA) (1:25 dilution; Dako, Glostrup, Denmark), LFABP (1:20 dilution; Abcam, Cambridge, UK), β-catenin (dilution 1:200; BD Biosciences, Franklin Lakes, New Jersey, USA) and glypican-3 (dilution 1:100; Biomosaics, Burlington, Vermont, USA). Glutamin synthetase staining was also performed routinely to improve the diagnostic accuracy of β-catenin inactivation.[20] For LFABP, staining was considered positive (+) when the protein was expressed in most tumorous hepatocytes, as well as in non-tumorous hepatocytes. SAA was considered positive when at least 10% of tumorous hepatocytes displayed cytoplasmic staining. β-Catenin positive staining corresponded to nuclear and cytoplasmic expression independently of the number of tumour stained hepatocytes. Staining for glutamine synthetase suggestive of β-catenin mutations was considered positive when a strong and diffuse expression was observed in the tumour. Glypican-3 staining was positive when tumour hepatocytes displayed membranous and/or cytoplasmic positivity, whatever the number of stained tumour cells.

Non-tumorous liver was also reviewed. Fibrosis was staged according to Kleiner *et al*[21]: no fibrosis (stage 0), zone 3 perisinusoidal or portal fibrosis (stage 1), perisinusoidal and portal fibrosis without bridging (stage 2), bridging fibrosis (stage 3) and cirrhosis (stage 4). Non-alcoholic fatty liver disease (NAFLD) was defined as any combination of steatosis, steatohepatitis (hepatocyte ballooning ± Mallory–Denk bodies, neutrophilic or mixed inflammatory infiltrates), and steatofibrosis. Non-alcoholic steatohepatitis lesions were defined according to the presence of steatosis, whatever its amount, and foci of ballooned cells and inflammatory infiltrates, as previously described.[21]

## RESULTS

### Demographics and time trend in incidence

The 23 patients of our own series whose HCA had evidence of malignant transformation were 16 men and seven women with a median age of 48 years (range 20–75). Of these, 20 patients had single HCA and three (all women) had more than one HCA including two patients with liver adenomatosis. Although the number of female patients whose HCA had malignant transformation has remained relatively constant during the study period, that of male patients has increased markedly since 2000 (figure 1). Over the entire study period, the incidence of malignant transformation was 4% in female and 47% in male.




| Malignancy in : | 1993-1995 | 1997-2000 | 2001-2004 | 2005-2008 |
|---|---|---|---|---|
| Single HCA male | 1 | 0 | 5 | 10 |
| Single HCA female | 0 | 2 | 1 | 1 |
| Multiple HCA female | 1 | 1 | 0 | 1 |

**Figure 1** Evolution of the numbers of female and male patients with benign and malignant hepatocellular adenoma seen over the study period divided into several time intervals (abscissa). Numbers in the table refer to patients with malignancy occurring in single and multiple hepatocellular adenoma. Only the 23 patients managed at our institution were included.

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### Associated conditions

All four female patients with single HCA had a history of hormonal treatment. Three aged 35–41 years, had prolonged use of OCs for 15, 19 and 20 years. The fourth patient, aged 54, had used OCs for less than 2 years, 25 years previously. No other potential risk factor was observed (table 1).

Both women with liver adenomatosis had been on OCs for 5 and 10 years and were in their late 30s. The female patient with multiple HCA had intrahepatic vascular disorders of unknown aetiology.

Four of the 16 male patients had an associated condition previously linked to HCA. This consisted in one substitutive treatment with androgen following autologous bone marrow transplantation, one Fanconi's anaemia with secondary haemochromatosis, and two users of recreational anabolic steroids (details on these were unavailable). All were less than 47 years old. Six of the 12 others, aged 52–75 years, fulfilled the WHO definition of metabolic syndrome including diabetes in all. One other patient with a BMI of 29 $kg/m^2$ and systemic hypertension had serological evidence of a healed HBV infection. The prevalence of a metabolic syndrome among men with no previously described risk factor was significantly higher than among women (6/12 vs 0/7, p=0.04).

### Characteristics of HCA with malignant changes

The median diameter of HCA with malignant transformation was 10 cm and only three were 5 cm or less. These were the 20-year-old man with ongoing androgen substitutive therapy (3 cm), the 45-year-old male patient with Fanconi's anaemia (4.5 cm) and the 54-year-old female with ancient and transient hormonal treatment (4.5 cm). Median diameters of HCAs associated with prolonged use of OCs (14 cm, range 6.5–19), a metabolic syndrome (10.5 cm, range 7–19), intrahepatic vascular disorders (11 and 15 cm), or no specific aetiology (in men 10.5 cm, range 7–18) were comparable.

Half of the HCAs (14/25) were of the telangiectatic/inflammatory SAA+ sub-type including five that additionally displayed cell atypias. Three other patients had cell atypias within their HCA but without inflammatory features. A single patient had a steatotic LFAP HCA (in a context of liver adenomatosis). The remaining seven patients had no specific features and were considered unclassified HCA. Immunostaining was consistent with β-catenin activation in two-thirds of HCA (16/25), including nine HCA with aberrant nuclear β-catenin staining and seven additional HCA with strong and diffuse glutamine synthetase staining. β-Catenin activation was present, in particular, in virtually all unclassified HCAs or HCAs with cell atypias and in approximately half of the telangiectatic/inflammatory HCAs (table 2). Both cell atypias within HCA and β-catenin activation were more frequent in men than in women (7/17 vs 1/8, p=0.16 and 14/17 vs 2/8, p=0.009, Fisher's exact test).

### Characteristics of HCC within HCA

Two main pathological patterns of malignant transformation of HCA were observed. It appeared either as well-defined macroscopic malignant nodules larger than 1 cm in eight patients or as randomly distributed microscopic foci in 17 patients (figure 2). Male patients more frequently had the microscopic pattern (14/17 vs 3/8 for women, p=0.03). HCC was well-differentiated in all but three patients with moderately differentiated tumours. Vascular extension and/or satellite nodules were present in two macroscopic type and one microscopic type HCC, but all HCA were larger than 15 cm. The serum α-fetoprotein level was moderately increased (200–400 ng/ml) in two patients with single HCA and markedly increased (2000–4000 ng/ml) in two patients with multiple HCA.

### Pathology of the non-tumorous liver

Significant changes were present in 14 patients (56%), including pathological changes of NAFLD (n=8), vascular lesions (nodular regenerative hyperplasia and obliterative portal venopathy, n=1 each), isolated fibrosis (stages 1 and 2, n=3) and diffuse iron overload (due to multiple transfusions for Fanconi's anaemia, n=1). Among patients displaying NAFLD, two had isolated steatosis (>33%), three had steatofibrosis (stages 1 and 2) and three had non-alcoholic steatohepatitis with fibrosis (stages 1 and 2). All three HCA with malignant transformation of 5 cm or less were associated with either stage 2 fibrosis (n=2) or iron overload (n=1). The β-catenin staining pattern was always normal in the non-tumorous liver (ie, membranous labelling of hepatocytes and biliary cells).

## DISCUSSION

We have reported the largest series of HCA with malignant transformation operated at a single institution. Although this is a selected population, we have highlighted a recent change in their epidemiology and analysed the pathological characteristics of both the underlying HCA and its malignant changes.

Most cases of HCA with malignant transformation have been reported in women. This is not surprising as women account for more than 90% of HCAs.[5 6 8] Incidence of malignant transformation in women whose HCA have been operated has recently been estimated to range between 3 and 4%.[5 6 8]

**Table 1** Clinical characteristics of 23 patients with malignant transformation within hepatocellular adenoma (HCA) stratified by number of HCA and gender. Two patients (one male and one female) operated at other institutions were excluded from this analysis

| Associated condition | Single | | Multiple | Age (years) |
|---|---|---|---|---|
| | Female (n=4) | Male (n=16) | Female (n=3) | Median (range) |
| OCs>2 years | 3 | – | 2 | 37 (35–41) |
| OCs<2 years | 1 | – | 0 | 54 |
| Androgens/steroids | – | 3 | – | (20–47) |
| Fanconi's anaemia/HBV | 0 | 2 | 0 | (45–70) |
| Vascular disorders | 0 | 1 | 1 | (30–67) |
| Metabolic syndrome | 0 | 6 | 0 | 62 (52–75) |

HBV, hepatitis B virus; OCs, oral contraceptives.

**Table 2** Pathological characteristics of hepatocellular adenoma (HCA) with malignant transformation in 25 patients stratified for number of HCAs and gender

| HCA subtype | Markers | | | Single HCA | | Multiple |
|---|---|---|---|---|---|---|
| | LFABP | SAA | β-cat/GS | Female | Male | Female |
| Steatotic | –ve | –ve | –ve | 0 | 0 | 1 |
| Inflammatory | +ve | +ve | –ve | 2 | 3 | 1 |
| | +ve | +ve | +ve | 1 | 7 | 0 |
| Cell atypias | +ve | –ve | +ve | 0 | 3 | 0 |
| Unclassified | +ve | –ve | –ve | 1 | 0 | 0 |
| | +ve | –ve | +ve | 0 | 4 | 0 |
| | nd | nd | –ve | 1 | 0 | 0 |
| | nd | nd | +ve | 0 | 0 | 1 |

β-cat/GS, immunostaining with both β-catenin and glutamine synthetase; nd, not determined.

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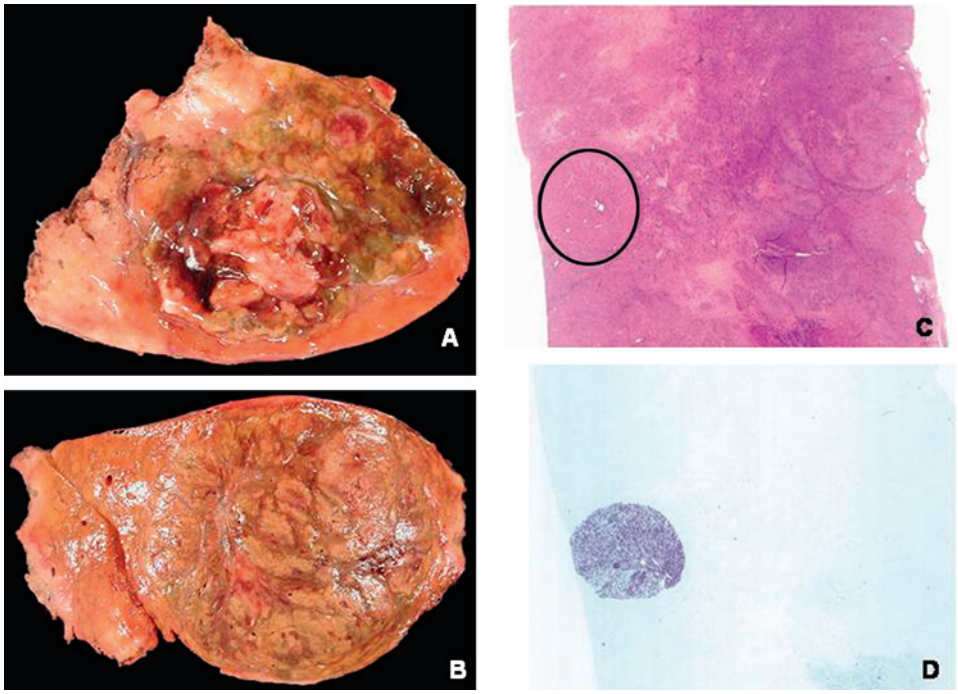


**Figure 2** Pathological analysis of hepatocellular adenoma (HCA) with malignant transformation. (A) Macroscopic view of HCA with macroscopic pattern of malignant transformation (HCA of 3 cm with a 1 cm heterogeneous malignant nodule), (B) Macroscopic view of HCA with microscopic pattern of malignant transformation (7 cm HCA of telangiectatic/inflammatory sub-type without malignant macroscopic nodule), (C, D) Mounted slide of the same HCA as in B showing a microscopic nodule (encircled) totally glypican-3 positive.

Our updated series confirms this figure (4%) and shows that it has remained remarkably constant during the study period. In men, HCA with malignant transformation but also HCA in general, have in contrast been considered anecdotic. In the multicentre North American series of 124 HCA patients, eight were men, one of whom had an HCA with malignant transformation.[8] Likewise, in the French series of Bordeaux in which they culled 128 patients, 12 were men and a single patient had HCA with malignant transformation.[5] This was also the case in the first part of our study (1990s) when men accounted for four of the 73 HCA patients and for a single case of HCA with malignant transformation. Since 2000, however, we have witnessed a marked increase in the number of male patients who had HCA with malignant transformation to a point that they currently outnumber females. With these increasing numbers, we have been able to estimate that the risk of malignant transformation of HCA in men is 47%, 10 times greater than in women.

The increase in the number of men who had evidence of malignancy within their HCA is unlikely to merely reflect a selection bias. It is both gender and time specific while the medical environment of our hospital has not changed. The most likely explanation is the emergence of HCA with malignant transformation associated with a metabolic syndrome. Among the 15 male patients observed since 2000 whose HCA had features of malignant transformation, four had rare but previously described gender-related specific aetiologies such as androgen treatment, Fanconi's anaemia [4] or use of recreational steroid.[22] One other had intrahepatic vascular disorders, as had one female patient and this has also been reported in other settings of hepatic vascular disease.[23] However, six of the 10 other men had a metabolic syndrome whereas this was never observed in women. This suggests that the metabolic syndrome is a new risk factor for malignant transformation within HCA and that HCC associated with the metabolic syndrome, which is a rising concern,[24] may develop from a pre-existing HCA rather than from regenerating nodules of an underlying liver disease. These hypotheses are in keeping with: (1) the marked increase in the incidence of the metabolic syndrome in the general population,[25] in particular in France during the study period;[25 26] (2) its association with a greater risk of liver cancer in men than in women,[27 28] as for HCC related to other aetiologies; and (3) the fact that HCCs associated with a metabolic syndrome are almost exclusively observed in men and most often occur in a background liver with limited histological changes apart from steatosis.[18] Previous observations that size and phenotype of HCA are the main risk factors for their malignant transformation also explain the male predominance as will be discussed below.

It is usually assumed that the risk of malignant transformation of an HCA increases as the tumour enlarges. Although their size has not been systematically reported, malignant changes have never been described in HCA less than 5 cm. The single exception in the literature is a 23-year-old woman whose 4 cm HCA showed multifocal malignant degeneration.[11] In our series of 25 patients whose HCA had malignant changes; three (12%) had HCA less than 5 cm. Two were men with specific aetiologies (androgen treatment and Fanconi's anaemia) including one with a 3 cm HCA which is the smallest reported so far. The third patient was a 54-year-old woman with a 4.5 cm HCA and no associated condition including no previous long-term use of OCs. In the remaining 22 patients, the median diameter was 11 cm (range 6–19 cm). Interestingly, HCA with malignant transformation occurred later in men with a metabolic syndrome than in women with prolonged OC (median age of 62 vs 35 years). As a matter of fact, evidence is accumulating that regression of HCA in women taking OCs is a slow but constant process.[5] For example, no HCA has been reported in women older than 66 years in the literature.[5 6 8] Furthermore, in a survey of HCC diagnosed in the greater Milan area, Italy, between 1984 and 1992, no woman aged 60 years or over had ever used OCs.[29] This does not appear to be the case in men with a metabolic syndrome whose HCA are unlikely to regress and will therefore be exposed to malignant changes for a more prolonged period.

Malignant transformation has also been correlated with the presence of β-catenin activation. A mutation of this gene is identified in 15–19% of normal HCA[6 15 16] but higher figures have been reported in HCAs with malignant transformation.



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This was initially described in five of 11 patients with HCC arising in HCA or borderline lesions[15] and subsequently in six out of six[5] and three out of eight[30] such patients. Using a combination of β-catenin and glutamin synthetase staining, which increases the accuracy of this detection, prevalence of the activation in our patients was 16 out of 25 (64%). Not unexpectedly, it was higher in men (82%) than in women (25%) as β-catenin-activated HCAs are more prevalent in men than in women.[15 16] This further explains the higher proportion of HCAs with malignant transformation that we have observed among men. The presence or absence of β-catenin activation in HCAs with malignant transformation was otherwise not correlated with other features such as HCA subtyping (except for the presence of cell atypias) or size.

HCC within HCA had two main characteristics. It was well differentiated in most patients (88%) and appeared as macroscopic nodules larger than 1 cm in one-third of the patients and in the remaining two-thirds as multiple microscopic foci. These features have previously been described[11] although their respective frequencies had not been quantified. We have, in addition, shown that the microscopic pattern was more frequent in men than in women. It is unclear at this stage if the microscopic and macroscopic patterns correspond to successive stages or to different processes of malignant transformation. Should microscopic areas progressively replace the whole HCA without forming discrete nodules, this would explain that evidence of a previous HCA within HCC associated with a metabolic syndrome has inconsistently been observed.

We acknowledge that our study focuses only on patients with simultaneous features of both HCA and HCC within the same tumour and overlook patients whose HCA have been completely replaced by the malignant transformation. However, our results suggest that the management of HCA could be tailored according primarily to gender. First, men are at a 50% risk of having malignant changes within their HCA and routine resection should therefore be considered irrespective of size. In the future, ablation may be considered as an alternative for those lesions smaller than 3 cm. Second, in women of childbearing age using OC, the risk of malignancy is low in general and hardly exists when the HCA is less than 5 cm. As rupture of HCA of this diameter is also very unlikely,[6 8] surveillance without resection may be sufficient. Third, women in their 50s or older or those whose HCA occurs in the absence of hormonal treatment might, as men, require more aggressive management. Should a conservative management be considered, biopsy of the HCA is useful to differentiate steatotic (LFABP negative) HCA that are at very low risk of bleeding[6] and malignancy from HCA with β-catenin activation, which are at increased risk of transformation.

**Competing interests** None.

**Ethics approval** This study was conducted with the approval of the local ethics committee.

**Contributorship statement** The six authors are justifiably credited with authorship, according to the authorship criteria. In detail: OF — conception, design, analysis and interpretation of data, drafting of the manuscript, final approval given; NF — acquisition of data, analysis and interpretation of data, final approval given; SD — acquisition of data, critical revision of manuscript, final approval given; JB — critical revision of manuscript, final approval given; PB — critical revision of manuscript, final approval given; VP — Conception, design, analysis and interpretation of data, drafting of the manuscript, final approval given.

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