

# IGFs and IGFBPs: surrogate markers for diagnosis and surveillance of tumour growth?

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## Abstract

**Insulin-like growth factors (IGFs), IGF receptors, and IGF binding proteins (IGFBPs) constitute the IGF system. Comprehensive data indicate that these factors play a pivotal role in tumorigenesis. Epidemiological data indicate that cancer risk is associated with high serum IGF-I values. Because dysregulation of the IGF system is a frequent pattern in malignancy, IGFs/IGFBPs might represent novel tumour markers that could be useful both for diagnosis and surveillance.**

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The insulin-like growth factor (IGF) system plays a crucial role in normal cell proliferation and malignant transformation.<sup>1,2</sup> It comprises IGF-I and IGF-II, the type I and type II receptors,<sup>3</sup> and a family of IGF binding proteins (IGFBPs) that specifically bind IGFs.<sup>4</sup> During the transition from the benign to the malignant state, qualitative and quantitative changes of the components of the IGF system are frequently observed. For example, increases in the type I IGF receptor are seen in human pancreatic cancer when compared with benign tissue.<sup>5</sup> Furthermore, IGFBP dysregulation also occurs in neuroblastoma,<sup>6</sup> nephroblastoma,<sup>7</sup> and acute lymphoblastic leukaemia,<sup>8</sup> among others. Thus, there is increasing evidence that IGFs and IGFBPs should be included in the panel of tumour markers used for histopathological diagnosis and serological surveillance procedures in various malignancies.

Paediatric tumours and syndromes (such as Beckwith-Wiedemann syndrome) associated with such tumours show increased IGF-II gene expression and transgenic mice overexpressing IGF-II have an enhanced risk of developing tumours.<sup>9</sup> Immunocytochemistry showed IGF-II in choroid plexus papillomas but not in normal human choroid plexus, suggesting that IGF-II is a useful marker for the differential diagnosis of choroid plexus papilloma.<sup>10</sup> IGF-II and H19, which is considered to be an oncofetal RNA and tumour suppressor gene,<sup>11</sup> are both imprinted genes located at 11p15. The H19 gene is expressed in tumours originating from tissues that express this gene in fetal life.<sup>12</sup> Thus, these factors show a tissue specific oncofetal pattern of expression.<sup>13</sup> In rhabdomyosarcoma, strong IGF-II mRNA expression was observed, which was inversely correlated with the degree of tumour cell differentiation. Various other soft tissue sarcomas showed no

IGF-II mRNA expression and it was concluded that IGF-II is a potential new marker for differential diagnosis of rhabdomyosarcoma.<sup>14</sup> There is evidence indicating that IGF-II plays a pivotal role in rhabdomyosarcoma tumorigenesis.<sup>15</sup> Coexpression of IGF-II mRNA with the Ki-67 proliferation marker in hepatocellular carcinoma suggests that IGF-II may play an important role in the development of this particular tumour.<sup>16</sup> In addition, the expression of H19 is under the control of the same regulatory genes as  $\alpha$  fetoprotein, which is a widely used tumour marker for hepatocellular carcinoma.<sup>12</sup> H19 was present in 13 of 18 cases, whereas staining for  $\alpha$  fetoprotein was positive in only nine of 18 cases.<sup>17</sup> Earlier reports indicated that H19 gene expression in human bladder carcinomas was associated with a more malignant grade.<sup>18</sup> It was suggested that H19 is an oncodevelopmental marker for bladder tumour progression and that this gene has oncogenic properties in this type of tumour.<sup>19</sup>

Raised serum IGFBP-1 values have been reported in patients with primary liver cancer<sup>20</sup> and ovarian cancer.<sup>21</sup> Whether these serum concentrations of IGFBP-1 are related to tumour cachexia or to production by the tumour itself is unclear. In the serum of patients with non-islet cell tumour hypoglycaemia, free IGF-I and IGF-II, in addition to IGFBP-1 and IGFBP-2 values, are raised.<sup>22</sup>

Consistently increased concentrations of IGFBP-2 have been described in serum and cyst fluids surrounding tumours of different histology, such as lung tumours,<sup>23</sup> Wilms's tumours,<sup>7</sup> prostate cancer,<sup>24,25</sup> colorectal tumours,<sup>26</sup> ovarian cancer,<sup>27,28</sup> acute lymphoblastic leukaemia,<sup>8</sup> and brain tumours.<sup>15</sup>

Increased IGF-I and decreased IGFBP-3 concentrations are found in patients with lung cancer in comparison with control subjects, so that measuring those factors might be useful for the assessment of lung cancer risk.<sup>29</sup> IGFBP-2 serum concentrations were significantly increased in patients with lung cancer compared with normal controls.<sup>30</sup>

## Prostate cancer

Plasma IGF-I is a predictor of prostate cancer risk.<sup>31</sup> High IGF-I and low IGF-II serum values are independently associated with increased risk of prostate cancer.<sup>32</sup> The IGF-I/prostate specific antigen (PSA) ratio significantly improved the detection of prostate cancer over the use of PSA alone.<sup>33</sup> Statin *et al* found an association between raised plasma IGF-I and increased prostate risk,<sup>34</sup> whereas Finne *et al* found no such association.<sup>35</sup> Another study showed a significant association between low serum concentrations of IGF-I and prostate cancer.<sup>36</sup> The biological importance of these

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data is less apparent. High IGF-I values may be associated with prostate cancer risk and the identification of raised serum IGF-I values might be useful in chemoprevention strategies. IGFBPs act as a storage pool and can inhibit or enhance IGF-mediated effects.<sup>37</sup> Increased production of IGFBP-2 by tumours may constitute an autocrine mechanism whereby enhanced tumour growth and invasion is maintained. There may be a possible role for tumour suppressor genes altered in malignancies leading to increased IGFBP-2 expression, thus increasing tumour invasiveness as a result of enhanced mitogenic action of IGF-I. Recently, a silencer domain of the rat IGFBP-2 gene that contains a target sequence for the retinoblastoma gene product was identified.<sup>38</sup> The raised serum concentrations of IGFBP-2 in patients with prostate cancer were related to the concentration of PSA,<sup>24</sup> which is also an IGFBP-3 protease and thus alters IGF-IGFBP-3 interactions.<sup>39</sup> Serum IGFBP-2 values were significantly higher in patients with prostate carcinoma and high PSA than in those with normal PSA.<sup>40</sup> High grade prostate intraepithelial neoplasia showed enhanced IGFBP-2 and IGFBP-3 mRNA expression, but IGFBP-3 protein concentrations were significantly decreased in malignant cells.<sup>41</sup> It appears that as prostate tissue progresses from the benign to the malignant state, IGFBP-2 immunoreactivity in the prostatic luminal epithelial cells increases and that of IGFBP-3 decreases.<sup>42</sup> IGFBP-5 immunoreactivity was also significantly increased in malignant prostate epithelium compared with benign epithelium.<sup>43</sup> Expression of IGFBP-2 and IGFBP-5 was higher, whereas IGFBP-3 was lower, in high versus low Gleason score prostate cancer.<sup>44</sup> It was also suggested that increases in IGF-I and intact IGFBP-3 values are positively associated with the presence of prostate carcinoma in patients with rather low PSA values, and that measurement of IGF-I and intact IGFBP-3 may be helpful for discriminating between prostate carcinoma and benign prostatic hyperplasia.<sup>45</sup> Clinical studies have been proposed to clarify whether measurement of IGF-I and IGFBP-3 in addition to PSA could improve the identification of men at high risk for prostate cancer.<sup>46</sup>

#### Colorectal cancer

Serum concentrations of IGF-II were increased in patients with colorectal adenomas compared with normal controls, indicating that IGF-II may be a tumour marker for these adenomas, which are known precursors of colorectal carcinomas.<sup>47</sup> IGFBP-2 was raised in patients with colorectal cancer and, in combination with carcinoembryonic antigen, showed high sensitivity for colorectal cancer, and could therefore be used for surveillance of cancer in patients with colorectal cancer.<sup>26</sup> IGFBP-2 mRNA expression is increased in human colorectal cancer cells, indicating that IGFBP-2 plays an autocrine role.<sup>48</sup> Increasing concentrations of IGFBP-1 were associated with a significant decrease in colorectal cancer

risk.<sup>49</sup> Therefore, high IGF-I and IGFBP-3 values may be markers for colorectal cancer risk.<sup>50</sup>

#### Breast cancer

The risk of breast cancer is reduced in women who experienced pre-eclampsia during pregnancy or who were born to a mother with pre-eclampsia. Pre-eclampsia is associated with hormonal alterations, including a reduction in IGF-I and an increase in IGFBP-1.<sup>51</sup> Thus, IGF-I and IGFBP-1 values could in this circumstance represent factors that determine a lifelong risk for breast cancer. Epidemiological studies have indicated an association between serum IGF-I values and cancer risk but have not established causality.<sup>52</sup> Lower serum concentrations of IGFBP-1, IGFBP-3, and IGFB-6 were found in patients with breast cancer, thus increasing the bioavailability of IGF-I.<sup>53</sup> The reduction of IGF-II after surgery for breast cancer was more pronounced in malignant tumours than in benign disease, and this was directly related to the size of the removed tumour.<sup>54</sup> It remains to be elucidated whether determination of IGF-II contributes to early detection of tumour recurrence.

#### Other cancers

Not only do ovarian cancer tissues express IGFBP-2 preferentially,<sup>55</sup> but the increased IGFBP-2 cyst fluid values mirror overproduction by the tumour itself, with IGFBP-2 mRNA expression being highest in invasive tumours.<sup>28</sup> IGFBP-2 concentrations correlated positively with the highly sensitive serum tumour marker, cancer antigen 125 (CA 125), in patients with ovarian cancer.<sup>56</sup>

Increased IGFBP-2 concentrations have also been reported in patients with acute lymphoblastic leukaemia<sup>57</sup> and, in general, increased serum IGFBP-2 concentrations coincide with higher detection rates of IGFBP-2 mRNA transcripts in leukaemia cells.<sup>8</sup> Previous investigations had suggested that high serum concentrations of IGFBP-2 in patients with acute lymphoblastic leukaemia may indicate an increased risk of relapse.<sup>58, 59</sup>

Patients with malignant brain tumours showed increased IGFBP-2 concentrations in cerebrospinal fluid and, furthermore, children with various peripheral tumours were found to have higher serum IGFBP-2 values, which returned to normal during complete remission.<sup>60</sup> In meningiomas, a high IGF-II/IGFBP-2 mRNA ratio has been depicted as a sign of biologically aggressive behaviour.<sup>61</sup> In gliomas, a highly significant correlation between IGFBP-2 cyst fluid values and immunohistochemistry and tumour grading was found.<sup>62</sup>

Patients with metastatic adrenocortical tumours had significantly higher IGFBP-2 plasma concentrations than normal controls and IGFBP-2 values in these patients were inversely correlated with their survival.<sup>63</sup> Tumour cell growth appears to be modulated by IGFBPs in different ways.<sup>64</sup>

In carcinoma in situ (CIS) of the testis, IGFBP-5 immunoreactivity was enhanced, so

that IGFBP-5 might be a novel tumour marker for CIS.<sup>65</sup> It needs to be established whether patients with tumours of the testis also have increased IGFBP-5 values in their serum.

In conclusion, IGFs and IGFs are secreted by several tumours and modulate their malignant behaviour. The genes encoding IGF-II and IGFBP-2 are upregulated in childhood malignancies, and these factors may therefore represent valuable tumour markers because they mirror the oncofetal pattern of expression.<sup>13</sup> The consistent correlation between IGFBP overexpression and tumour grading or invasiveness could indicate their usefulness as a potential prognostic factor, which might predict outcome. Because of the pronounced expression of the IGF system seen during malignant transformation, these factors may also represent targets for therapeutic intervention.

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