Hyperglycosylated hCG and Its Free ß-Subunit Drives Malignancy

Laurence A. Cole*

hCG Reference Service, Angel Fire, NM 87710, USA

Abstract: Tumor marker studies were conducted measuring 2,277 malignancies using a cut-off of 3 fmol/ml. As found 110 of 110 trophoblastic malignancies or 100% were positive for ß-core fragment an hCG serum degradation product. Just 949 of 2167 (44%) of non-trophoblastic or other cancers were positive using this 3 fmol/ml cut-off. When the cut-off of the assay was lowered to 0.1 fmol/ml, or lowered by 30-fold 100% of non-trophoblastic or other cancers were detected, or all cancers were detected.

What do cancers secrete. Cancer were tested with three immunoassays, Immulite total hCG, B152 hyperglycosylated hCG and FBT11 free ß-subunit, serum of 34 trophoblastic cancers and 32 non-trophoblastic cancers were tested. A total of 34 of 34 trophoblastic cancer produced primarily hyperglycosylated hCG (B152 hyperglycosylated assay 96%±12% of Immulite), and 32 of 32 non-trophoblastic cancers produced primarily hyperglycosylated hCG free ß-subunit (B152 hyperglycosylated assay 102%±6.2% of Immulite, FBT11 free ß-subunit assay 128%±10% of Immulite).

Seven independent laboratories each showed with a wide mixture of cancers (patient tissue and cancer cell lines) that ß-subunit promoted malignancy (cell growth, cell invasion and blockage of apoptosis) in cancer cells. I then showed that hyperglycosylated hCG and its ß-subunit promoted malignancy in 10 different cancer cell lines.

I then tied my data and the seven independent laboratory data together and concluded that hyperglycosylated hCG and its ß-subunit drove malignancy in all or most cancers.

Keywords: Hyperglycosylated hCG, hCG and Malignancy.

INTRODUCTION

I have now proven [1-4], along with the seven confirmatory studies by independent laboratories [5-12], that hyperglycosylated hCG and its free ß-subunit drive malignancy in all or most human cancers. Since malignancy makes a cancer cancerous, hyperglycosylated hCG and its free ß-subunit drives all or most human cancers. Here we review carefully all the data showing that hyperglycosylated hCG and its free ß-subunit drives malignancy in human cancers [1-12].

1. THE HORMONE hCG AND THE AUTOCRINE HYPERGLYCOSYLATED hCG

The hCG α- and ß-subunit genes make two totally separate glycoproteins, the hormone hCG (known as the pregnancy hormone) and the autocrine hyperglycosylated hCG. The three-dimensional structures of these two molecules is shown in Figure **1**, from the three-dimensional modelling of Lustbader [13], Wu [14] and Lapthorn [15] and the thermodynamic modelling of Butler *et al.* [16].

As shown, the hormone hCG and the autocrine hyperglycosylated hCG are 97.2% identical. The only difference is in the three O-linked oligosaccharides at ß121, ß127 and ß132, and in the three-dimensional folding of the ß-subunit C-terminal peptide (Figure **1**).

*Address correspondence to this author at the hCG Reference Service, P.O. Box 950, Angel Fire, NM 87710, USA; Tel: 575-377-1330;
E-mail: larry@hcglab.com

Studies show that the autocrine hyperglycosylated hCG is processed before receptor binding, it is first cleaved or nicked by leukocyte elastase, and then dissociates releasing the ß-subunit, it is the ß-subunit of hyperglycosylated hCG which acts on the transforming growth factor receptor [6,17,18] (Figure **2**). Interestingly, the hormone hCG is not cleaved or dissociated before binding the luteinizing hormone (LH)/hCG joint hormone receptor. In fact the cleaved and dissociated molecule is not recognized by the LH/hCG receptor.

As a result of this processing, the hormone hCG alone binds the LH/hCG hormone receptor, while the autocrine hyperglycosylated hCG ß-subunit, the autocrine hyperglycosylated hCG nicked ß-subunit, and the hormone hCG ß-subunit [16] binds the TGF-ß receptor, TGF-ß is the direct ancestor of hCG α- and ß-subunit [19,20].

Trophoblastic cancers produce hyperglycosylated hCG and non-trophoblastic cancers or other cancers produce hyperglycosylated hCG free ß-subunit. Although the TGF-ß receptor binds hyperglycosylated hCG ß-subunit, I asked why do non-trophoblastic and other cancers produce only a hyperglycosylated hCG free ß-subunit and not a dimeric αß molecule?

Beebe *et al*. [21] provides a simple explanation as to why non-trophoblastic and other cancers only produce a free ß-subunit. A trophoblast cell disulfide isomerase adds the final two disulfide bonds, ß93-ß100

ISSN: 1927-7210 / E-ISSN: 1927-7229/18

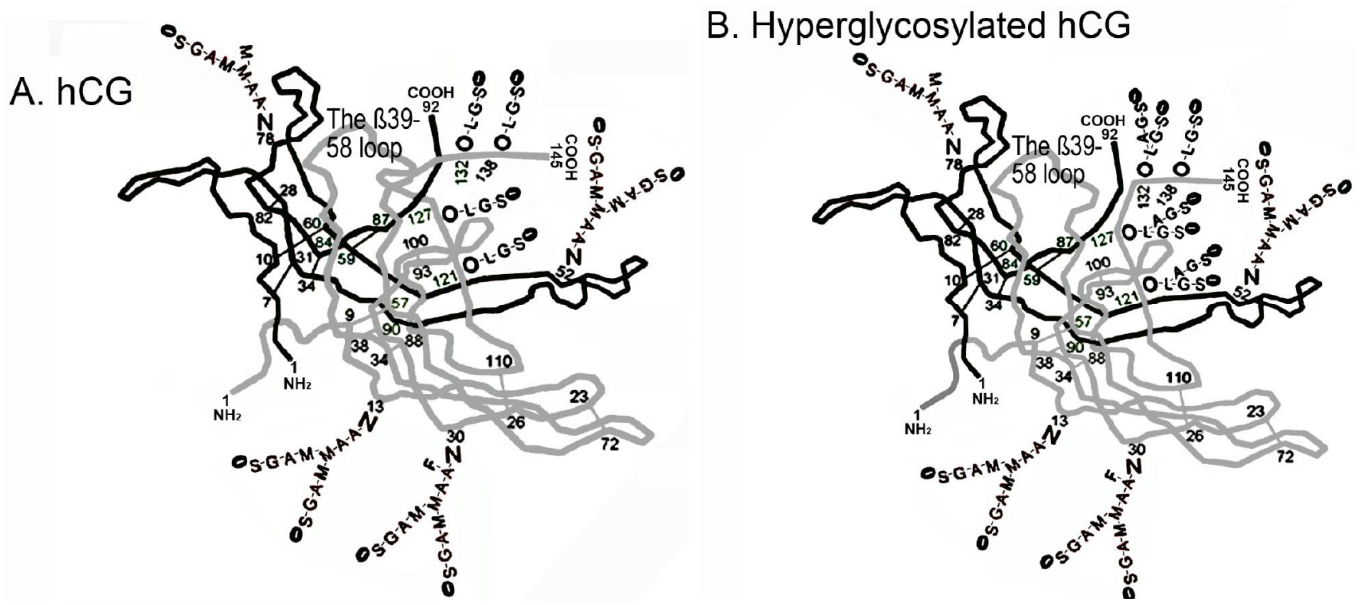

Figure 1: Three-dimensional structure of the hormone hCG and the autocrine hyperglycosylated hCG. The α-subunit is shown in black and the ß-subunit in grey.

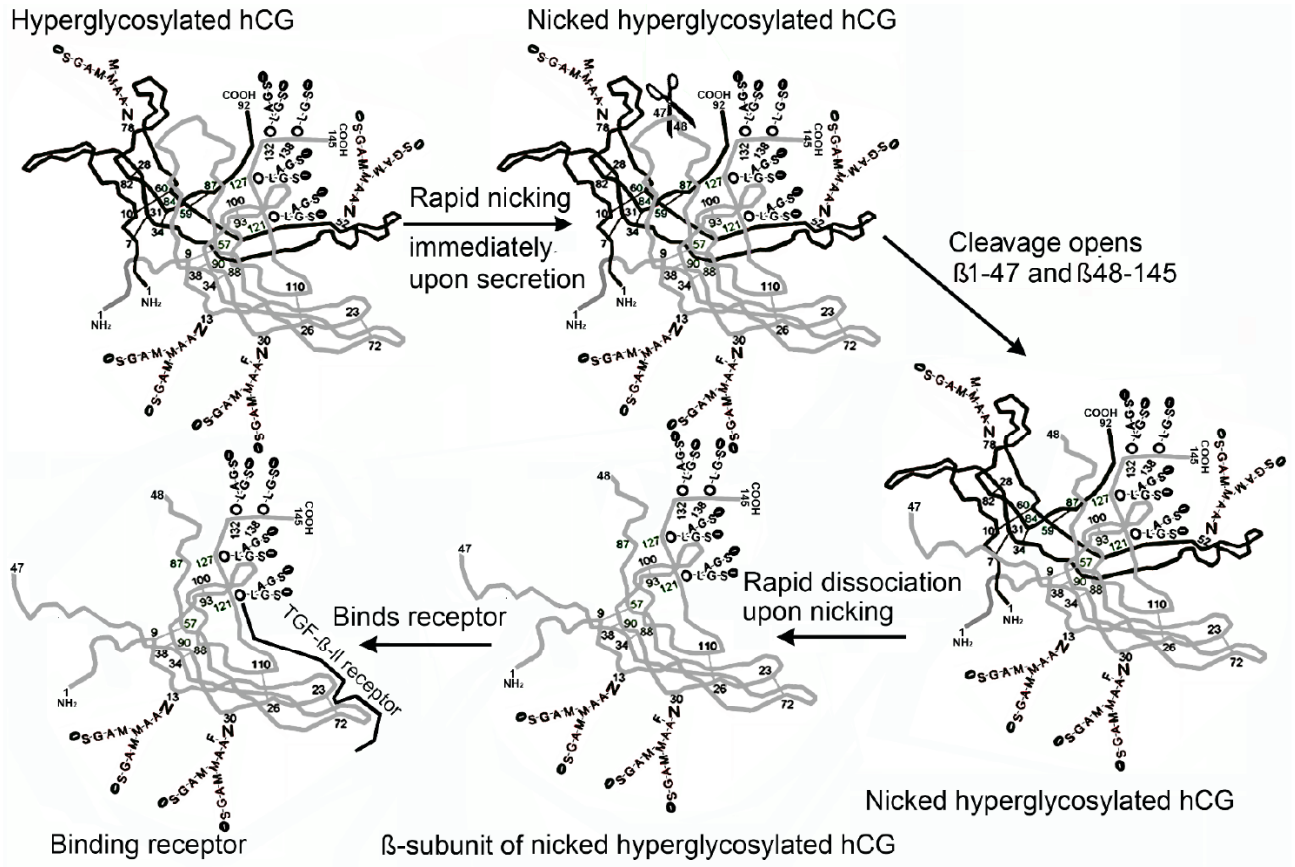

Figure 2: The processing of hyperglycosylated hCG before receptor binding.

and ß26-ß110 on trophoblast cell ß-subunit. In the absence of this enzyme in non-trophoblastic cancers, these disulfide bridges become absent and with the absence of these disulfide bridges ß-subunit is not recognized by α-subunit for combination and only a free ß-subunit is produced. This happens with production by non-trophoblastic cancers. The cells do not make the trophoblast cell disulfide isomerase and do not make the last two disulfide bridges. As such the cells only make a free ß-subunit [21].

Table 1: The Use of Urine ß-Core Fragment as a Tumor Marker (B204 Assay, ß-Core + ß-Subunit)

Source	First Morning Urine, B204 Assay ß-core + ß-subunit		
	Cut-off >3 fmol/ml		
	#Cases	#Positive	Sensitivity
A. Trophoblastic malignancies			
Choriocarcinoma	63	63	100%
Ovarian germ cell cancer	11	11	100%
Testicular germ cell cancer	17	17	100%
Total	**110**	**110**	**100%**
B. Non-trophoblastic malignancy			
Bladder cancer	140	62	44%
Breast cancer	456	156	34%
Cervical cancer	410	197	48%
Colorectal cancer	80	29	36%
Endometrial cancer	233	103	44%
Gastric cancer	205	90	44%
Hepatic cancer	46	21	44%
Lung cancer	154	38	25%
Intestinal cancer	17	8	47%
Lymphoma	41	13	32%
Ovarian cancer	207	145	70%
Pancreatic cancer	29	16	55%
Prostate cancer	12	9	75%
Renal cancer	66	32	48%
Uterine cancer	63	26	41%
Vulvar cancer	8	4	50%
Total	**2167**	**949**	**44%**
C. Healthy			
NED, post cancer chemotherapy	33	2	6%
NED, post cancer surgery	21	1	5%
Healthy female, no cancer history	72	2	3%
Healthy male, no cancer history	28	1	4%
Total	**154**	**6**	**4%**
D. Benign Disease			
Benign gynecological lesion, tumor	28	0	0%
Follicular ovarian cyst, benign	71	1	0%
Benign ovarian cyst, non-functional	26	0	0%
Cervical carcinoma in-situ	12	0	0%
Cervical dyskaryosis	66	2	0%
Condyloma	30	0	0%
Endometriosis	16	1	0%
Myoma	27	3	0%
Total	**276**	**7**	**0%**

Table 2: Fifty-Six New Ovarian Cancer Cases Tested with a More Sensitive ß-Core Fragment Test

Case	Pathologic Diagnosis	Stage	Status	ß-core fragment
1	Ovarian Endometrioid carcinoma	IV	Persistent	0.12
2	Ovarian Endometrioid carcinoma	IV	New, not treated	0.15
3	Ovarian Serous cystadenocarcinoma	IIIc	New, not treated	0.20
4	Ovarian Serous cystadenocarcinoma	IIIc	Persistent	0.20
5	Ovarian Serous cystadenocarcinoma	IIIc	Recurrent	0.25
6	Ovarian Serous cystadenocarcinoma	IV	Recurrent	0.40
7	Ovarian Serous cystadenocarcinoma	IV	Recurrent	0.40
8	Ovarian Brenner tumor	Ia	New, not treated	0.58
9	Ovarian Serous cystadenocarcinoma	IIIc	New, not treated	0.60
10	Ovarian Serous cystadenocarcinoma	IIIc	New, not treated	0.75
11	Ovarian Brenner tumor	Ia	New, not treated	0.88
12	Ovarian Serous cystadenocarcinoma	IIIc	Recurrent	1.2
13	Ovarian Granulosa-theca cell malignancy	II	Recurrent	1.6
14	Ovarian Serous cystadenocarcinoma	IIIc	Recurrent	2.1
15	Ovarian Endometrioid carcinoma	III	Recurrent	2.3
16	Ovarian Serous cystadenocarcinoma	IIIc	Persistent	2.5
17	Ovarian Mucinous	Ia	New, not treated	3.1
18	Ovarian Endometrioid carcinoma	IIIc	Recurrent	3.1
19	Ovarian Serous cystadenocarcinoma	II	New, not treated	3.5
20	Ovarian Granulosa-theca cell malignancy	IIIc	Persisent	3.7
21	Ovarian Mucinous cystadenocarcinoma	III	Recurrent	4.2
22	Ovarian Serous cystadenocarcinoma	III	New, not treated	4.5
23	Ovarian Serous cystadenocarcinoma	III	New, not treated	4.3
24	Ovarian Clear cell carcinoma	IIIc	New, not treated	4.8
25	Ovarian Clear cell carcinoma	IIIc	Recurrent	5.5
26	Ovarian Serous cystadenocarcinoma	IIIc	New, not treated	6.3
27	Ovarian Serous cystadenocarcinoma	IIIc	New, not treated	6.6
28	Ovarian Mixed epithelial tumor	IIIc	New, not treated	7.1
29	Ovarian Mixed epithelial tumor	III	New, not treated	7.9
30	Ovarian Serous cystadenocarcinoma	IIIc	Persistent	8.8
31	Ovarian Serous cystadenocarcinoma	III	Persistent	9.5
32	Ovarian Mixed epithelial tumor	IIIc	New, not treated	10
33	Ovarian Mixed epithelial tumour	IIc	New, not treated	11
34	Ovarian Serous cystadenocarcinoma	IIb	New, not treated	11
35	Ovarian Serous cystadenocarcinoma	III	New, not treated	11
36	Ovarian Serous cystadenocarcinoma	IV	Recurrent	12
37	Ovarian Serous cystadenocarcinoma	IV	Recurrent	12
38	Ovarian Endometrioid carcinoma	III	New, not treated	12
39	Ovarian Endometrioid carcinoma	III	Persistent	13
40	Ovarian Mixed mesodermal carcinoma	III	Recurrent	14
41	Ovarian Mixed mesodermal carcinoma	IV	Recurrent	16

(Table 2). Continued.

Case	Pathologic Diagnosis	Stage	Status	ß-core fragment
42	Ovarian Serous cystadenocarcinoma	IIc	Recurrent	16
43	Ovarian Serous cystadenocarcinoma	IV	Recurrent	17
44	Ovarian Serous cystadenocarcinoma	IIIc	New, not treated	18
45	Ovarian Serous cystadenocarcinoma	IIIc	Persistent	20
46	Ovarian Mixed epithelial tumor	IIIc	Recurrent	20
47	Ovarian Mixed epithelial tumor	III	Recurrent	21
48	Ovarian Serous cystadenocarcinoma	IV	New, not treated	21
49	Ovarian Serous cystadenocarcinoma	IV	New, not treated	24
50	Ovarian Serous cystadenocarcinoma	III	New, not treated	28
51	Ovarian Serous cystadenocarcinoma	IIb	New, not treated	29
52	Ovarian Malignant dermoid cyst/teratoma	IIb	New, not treated	32
53	Ovarian Serous cystadenocarcinoma	III	New, not treated	33
54	Ovarian Serous cystadenocarcinoma	IIIc	New, not treated	41
55	Ovarian Serous cystadenocarcinoma	IV	Recurrent	54
56	Ovarian Mixed epithelial tumor	IV	New, not treated	59

2. hCG AS A TUMOR MARKER

For many years, 1970-2018 hCG and its ß-subunit have been used as a general tumor marker for human cancers [22-28], with hundreds of papers describing hCG and ß-subunit production by different cancers [22-28]. I tested hCG ß-subunit as a tumor in 2,277 cancer cases collected from 1985 to 1999. I measured the serum degradation product of hyperglycosylated hCG and its ß-subunit, first morning urine ß-core fragment (Table **1**).

As shown, I detected 110 of 110 or 100% of cases of trophoblastic cancers and 949 of 2167 or 44% of non-trophoblastic cancer or other cases. The cut-off used for detecting cancer was 3 fmol/ml. At this cut-off few healthy individual or individual with benign disease were detected, 13 cases out of 430 or 3.0%.

What does 44% detection mean? Surely a specific cancer either produces or does not produce hCG. I produced a much more sensitive ß-core fragment test, cut-off 0.10 fmol/ml. I then in 2000 tested it with 56 new ovarian cancer cases (Table **2**). All 56 of 56 or 100% of non-trophoblastic cancer were detected. One hundred percent detection made more sense for non-trophoblastic cancer. I then tested 60 pancreatic cancers and 52 cervical cancer with this more sensitive tumor marker assay. Once again we confirmed 100% detection using a more sensitive test. It appears the 100% of non-trophoblastic cancers produce a form of hCG.

The studies of Acevedo *et al*. [29] and Regelson [30] used a double antibody method with flow cytometry techniques to examine the expression of hCG ß-subunit by cancer cells. They showed that 100% of non-trophoblastic or other cancer cells expressed the ß-subunit gene. This very much confirms our combined conclusion, that 100% of cancer produce hCG, hCG ß-subunit or their serum degradation product, ß-core fragment.

3. STRUCTURE OF CANCER hCG

Multiple investigators reported that cancer cells were positive in an hCGß assay [22-28], or that cancer cells produce hCG free ß-subunit [22-28,31,32]. What actual structure hCG molecules do cancers produce? I measured by immunoassays concentration using the Siemens Immulite 1000 total hCG assay, detects equally: hyperglycosylated hCG, hormone hCG, hyperglycosylated hCG ß-subunit and hormone hCG ß-subunit. Using the B152 hyperglycosylated hCG assay, detects hyperglycosylated hCG and its ß-subunit. Using the FBT11 free ß-subunit assay, detects equally, hormone hCG free ß-subunit and hyperglycosylated hCG free ß-subunit.

As shown in Table **3**, I tested 32 serum samples from different trophoblastic cancers, and 34 serum samples from different non-trophoblastic or other cancers. As shown all 32 trophoblastic cancer tested produced primarily hyperglycosylated hCG (B152

Table 3: Content of Cancer Patient Serum, Measured Using Immulite Total hCG Assay, B152 Hyperglycosylated Molecule Assay, and FBT11 Free ß-Subunit Assay

Case or sample	Immulite 1000 assay (Total hCG assay)	B152 assay (Hyperglycosylated molecules assay)		FBT11 assay (Free ß-subunit assay)	
	ng/ml	ng/ml	% total hCG	ng/ml	% total hCG
Standards					
Recombinant hCG (Ovidrel), 1000 ng/ml	1007	0.13	0.013%	1.17	0.12%
Recombinant hCG ß-subunit, 600 ng/ml	602	0.11	0.011%	615	102%
Hyperglycosylated hCG C5, 1000 ng/ml	997	995	100%	14	1.4%
C5 free ß-subunit standard, 600 ng/ml	578	687	100%	610	106%
Trophoblastic cancers					
Choriocarcinoma case 3, pre-therapy	21,200	23,300	110%	1,172	5.5%
Choriocarcinoma case 7, pre-therapy	33,700	34,700	103%	1,610	4.8%
Choriocarcinoma case 8, pre-therapy	57,400	54,600	95%	5,680	9.9%
Choriocarcinoma case 11, pre-therapy	20,600	19,900	97%	2,010	9.8%
Choriocarcinoma case 12, pre-therapy	27,500	30,100	109%	5,330	19%
Choriocarcinoma case 23, pre-therapy	153,400	155,000	101%	15,740	10%
Choriocarcinoma case 25, pre-therapy	34,700	36,800	106%	1,230	3.5%
Choriocarcinoma case 26, pre-therapy	43,400	47,700	110%	1,250	2.9%
Choriocarcinoma case 32, pre-therapy	210,500	210,200	100%	15,750	7.5%
Choriocarcinoma case 36, during therapy	2,500	2,100	84%	155	6.2%
Choriocarcinoma case 41, during therapy	3,700	2,900	78%	505	14%
Choriocarcinoma case 42, during therapy	1,600	870	54%	360	23%
Choriocarcinoma case 47, during therapy	9,900	9,900	100%	1,260	13%
Choriocarcinoma case 48, during therapy	20,400	19,000	93%	1,880	9.2%
Choriocarcinoma case 49, during therapy	1,600	1,010	63%	29	1.8%
Choriocarcinoma case 50, during therapy	1,100	1,010	91%	106	9.6%
Choriocarcinoma case 54, during therapy	3,300	2,500	76%	230	7.0%
Choriocarcinoma case 57, during therapy	3,600	3,100	86%	410	11%
Choriocarcinoma case 69, during therapy	1,050	1,050	100%	89	8.5%
Choriocarcinoma case 61, during therapy	6,300	5,900	94%	311	4.9%
Ovarian germ cell cancer 1, pre-therapy	13,400	14,000	104%	2,230	17%
Ovarian germ cell cancer 4, pre-therapy	8,800	8,800	100%	547	6.2%
Ovarian germ cell cancer 5, pre-therapy	17,600	17,100	97%	3,120	18%
Ovarian germ cell cancer 6, pre-therapy	33,400	34,300	102%	11,560	34%
Ovarian germ cell cancer 7, pre-therapy	18,900	18,700	99%	196	1.0%
Ovarian germ cell cancer 11, pre-therapy	16,200	16,100	99%	151	0.9%
Testicular germ cell cancer 7, pre-therapy	10,400	10,600	102%	655	6.3%
Testicular germ cell cancer 9, pre-therapy	14,500	14,700	99%	907	6.3%
Testicular germ cell cancer 10, pre-therapy	19,100	19,300	101%	430	2.3%
Testicular germ cell cancer 11, pre-therapy	11,000	11,100	101%	`1,220	11%
Testicular germ cell cancer 14, pre-therapy	9,200	9,500	103%	103	1.1%
Testicular germ cell cancer 17, pre-therapy	13,700	14,300	104%	2,240	16%
Mean ± standard deviation			96%±12%		9.3%±7.1%

(Table 3). Continued.

Case or sample	Immulite 1000 assay (Total hCG assay)	B152 assay (Hyperglycosylated molecules assay)		FBT11 assay (Free ß-subunit assay)	
	ng/ml	ng/ml	% total hCG	ng/ml	% total hCG
Non-trophoblastic cancers					
Bladder cancer case 14	0.09	0.09	100%	0.10	111%
Bladder cancer case 77	0.09	0.10	111%	0.09	100%
Bladder cancer case 120	0.12	0.12	100%	0.11	92%
Bladder cancer case 121	0.15	0.15	100%	0.15	100%
Bladder cancer case 169	1.3	1.4	108%	1.4	108%
Breast cancer case 1	1.3	1.3	100%	1.0	77%
Breast cancer case 6	0.09	0.10	111%	0.11	122%
Breast cancer case 23	0.11	0.11	100%	0.12	109%
Breast cancer case 32	0.66	0.62	94%	0.71	108%
Breast cancer case 33	0.11	0.12	109%	0.11	100%
Breast cancer case 37	0.14	0.14	100%	0.15	107%
Breast cancer case 48	0.11	0.10	91%	0.10	91%
Breast cancer case 40	0.09	0.09	100%	0.10	111%
Breast cancer case 42	0.12	0.13	108%	0.10	83%
Cervical cancer case 5	0.13	0.13	100%	0.13	100%
Cervical cancer case 8	0.17	0.18	106%	0.18	106%
Cervical cancer case 14	0.14	0.15	107%	0.14	100%
Cervical cancer case 23	0.18	0.19	106%	0.18	100%
Cervical cancer case 26	0.17	0.16	94%	0.17	100%
Cervical cancer case 32	0.34	0.36	106%	0.35	103%
Cervical cancer case 36	0.18	0.18	100%	0.20	111%
Cervical cancer case 41	0.44	0.46	105%	0.40	91%
Cervical cancer case 48	0.18	0.19	106%	0.18	100%
Cervical cancer case 60	0.14	0.16	114%	0.12	86%
Endometrial cancer case 11	0.16	0.16	100%	0.14	88%
Endometrial cancer case 21	0.36	0.38	106%	0.32	89%
Endometrial cancer case 53	0.09	0.09	100%	0.10	111%
Ovarian cancer case 2	0.23	0.24	104%	0.23	100%
Ovarian cancer case 25	0.14	0.13	93%	0.15	107%
Ovarian cancer case 48	0.11	0.10	91%	0.10	91%
Ovarian cancer case 82	0.10	0.11	110%	0.10	100%
Ovarian cancer case 143	0.10	0.09	90%	0.08	80%
Vulvar cancer case 13	0.27	0.28	104%	0.23	85%
Vulvae cancer case 39	0.13	0.13	100%	0.12	92%
Mean ± standard deviation			102%±6.2%		128%±10%

hyperglycosylated assay 96%±12% of Immulite total hCG), and all 34 varied non-trophoblastic cancers produced primarily hyperglycosylated hCG free ß-subunit (B152 hyperglycosylated assay 102%±6.2% of Immulite total hCG, FBT11 free ß-subunit assay 128%±10% of Immulite total hCG). As shown by Beebe

et al. [21] this dimer/monomer difference is because the non-trophoblastic cells do not produce the needed trophoblast disulfide isomerase. As such they do not form disulfide linkages properly on ß-subunit and so this subunit does not combine with α-subunit.

A study of dimers vs. monomer showed that non-trophoblastic cells could be promoted by either hyperglycosylated hCG or hyperglycosylated hCG ß-subunit [4].

4. THE SEVEN INDEPENDENT CONFORMATIONAL STUDIES

Research by Gillott *et al*. [5] in 1996 changed the approach to hyperglycosylated hCG, hyperglycosylated hCG ß-subunit and cancer. It showed with cultured bladder cancer cells that ß-subunit produced by cancer cells promoted cancer cell growth, and blocked cancer cell apoptosis, or promoted malignancy in the cancer cells (Table **4**). In 2000 this research was repeated and

Table 4: Reports that Hyperglycosylated hCG and its ß-Subunit Promoted Malignancy in Cancer Cells

Year	Author	Cancer cell tested	Promotes cancer cell growth	Promotes cancer cell invasion	Blocks cancer cell apoptosis	Ref
1996	Gillott *et al*.	T24 Epithelial bladder cancer cell line	X		X	5
		ScaBER squamous bladder cancer cell line	X		X	
		RT112 bladder carcinoma cell line	X		X	
		5637 adherent bladder carcinoma cell line	X		X	
2000	Butler *et al*.	ScaBER squamous bladder cancer cell line	X		X	6
2002	Devi *et al*.	DU145 prostate carcinoma cells	X			7
2006	Cole *et al*.	Jar choriocarcinoma cell line	X	X		8
		JEG-III choriocarcinoma cell line	X	X		
2008	Jankowska *et al*.	12 patients with planoepithelial cervical cancer			X	9
		1 patient with glossy cell cervical cancer			X	
		1 patient with Basaloid cell cervical cancer			X	
		1 patient with Intraepitheliate cervical cancer			X	
		15 patients with endometrial cancer			X	
2008	Li *et al*.	81 patients with uterine cervical cancer			X	10
2011	Guo *et al*.	T29 ovarian epithelial carcinoma cell line	X		X	11
		T80 ovarian epithelial carcinoma cell line	X		X	
		15 patients with ovarian carcinoma	X		X	
2018	Kawamata *et al*.	80 patients with colorectal cancer	X	X		12
		Caco-2 epithelial colorectal cancer	X	X		
		LoVo epithelial colorectal cancer	X	X		
		HCA-7 epithelial colorectal cancer	X	X		
		WiDr colorectal adenocarcinoma	X	X		
		T84 epithelial colorectal cancer	X	X		
2017	Cole	Jar choriocarcinoma cell line	X	X		1-4
		JEG-III choriocarcinoma cell line	X	X		
		NTERA germ cell testicular cancer cell line	X			
		Hec-1-a endometrial carcinoma cell line	X			
		ScaBER squamous bladder cancer cell line	X			
		KLE endometrial adenocarcinoma cell line	X			
		SK-MES-1 epithelial lung carcinoma cell line	X			
		KM-H2 Hodgkin's lymphoma cell line	X			
		T24 epithelial bladder cancer cell line	X			
		CasKi epithelial cervical carcinoma cell line	X			

confirmed by Butler *et al*. showing once more that ß-subunit produced by cancer cells promoted cancer cell growth, and blocked cancer cell apoptosis, or promoted malignancy in the cancer cells [6] (Table **4**). Then in 2002 Devi *et al*. repeated this work and showed the same thing, that ß-subunit produce by prostate cancer cells promoted cancer cell growth and cancer cell invasion, or cancer cell malignancy [7] (Table **4**). In 2006, I repeated the work and showed the same thing with trophoblastic cancers, that hyperglycosylated hCG produced by trophoblastic cancers promoted cancer cell growth and promoted cancer cell invasion, or malignancy [8] (Table **4**).

Then in 2008 Jankowska *et al*. [9] repeated the work and showed that ß-subunit produced by 15 patients with cervical cancer and 15 patients with endometrial cancer blocked cancer cell apoptosis or promoted malignancy (Table **4**). In 2008 Li *et al*. [10] showed with 81 patients with uterine cancer that the ß-subunit blocked an important part of malignancy, or cancer cell apoptosis (Table **4**). In 2011 Guo *et al*. [11] showed the same thing, that ß-subunit promoted cell growth and blocked cancer cell apoptosis or promoted malignancy in 15 patients with ovarian cancer and two ovarian cancer cell lines (Table **4**). Finally, in 2018 Kawamata *et al*. [12] showed with 80 patients with colorectal cancer and 5 colorectal cancer cell lines that ß-subunit promoted cancer cell growth and promoted cancer cell invasion or promoted malignancy.

In 2012, 2015 and 2017 I demonstrated that hyperglycosylated hCG and hyperglycosylated hCG ß-subunit promoted cell growth or promoted cancer cell malignancy using 10 varied cancer cell lines (Table **5**): JAR and JEG-3 placental choriocarcinoma, NTERA

Table 5: Promotion of Cancer Cell 24 h Growth at 70% Confluency by C5 Hyperglycosylated hCG (Trophoblastic Cancers) and its ß-Subunit (Non-Trophoblastic Cancers)

Cells	Supplement added to culture fluid	% effect on cell count	T test
Jar choriocarcinoma	No additive Hyperglycosylated hCG 20 ng/ml Hyperglycosylated hCG 200 ng/ml	100% cell count after 24 h 112% cell count after 24 h 130% cell count after 24 h	P=0.0123
JEG-3 choriocarcinoma	No additive Hyperglycosylated hCG 20 ng/ml Hyperglycosylated hCG 200 ng/ml	100% cell count after 24 h 110% cell count after 24 h 128% cell count after 24 h	P=0.0018
NTERA Testicular germ cell	No additive Hyperglycosylated hCG 20 ng/ml Hyperglycosylated hCG 200 ng/ml	100% cell count after 24 h 118% cell count after 24 h 132% cell count after 24 h	P=0.0018
Hec-1-a Endometrial adenocarcinoma	No additive Hyperglycosylated hCG ß-subunit 20 ng/ml Hyperglycosylated hCG ß-subunit 200 ng/ml	100% cell count after 24 h 138% cell count after 24 h 166% cell count after 24h	P=0.0021
ScaBER squamous bladder cancer	No additive Hyperglycosylated hCG ß-subunit 20 ng/ml Hyperglycosylated hCG ß-subunit 200 ng/ml	100% cell count after 24 h 150% cell count after 24 h 156% cell count after 24h	P=0.010
KLE Endometrial adenocarcinoma	No additive Hyperglycosylated hCG ß-subunit 20 ng/ml Hyperglycosylated hCG ß-subunit 200 ng/ml	100% cell count after 24 h 117% cell count after 24 h 132% cell count after 24 h	P=0.0.001
SK-MES-1 Epithelial lung cancer	No additive Hyperglycosylated hCG ß-subunit 20 ng/ml Hyperglycosylated hCG ß-subunit 200 ng/ml	100% cell count after 24 h 134% cell count after 24 h 163% cell count after 24 h	P=0.005
KM-H2 Hodgkin's Lymphoma cells	No additive Hyperglycosylated hCG β-subunit 20 ng/ml Hyperglycosylated hCG ß-subunit 200 ng/ml	100% cell count after 24 h 120% cell count after 24 h 145% cell count after 24 h	P=0011
T24 Bladder epithelial carcinoma	No additive Hyperglycosylated hCG β-subunit 20 ng/ml Hyperglycosylated hCG ß-subunit 200 ng/ml	100% cell count after 24 h 110% cell count after 24 h 128% cell count after 24 h	P=0.123
Caski epithelial cervical carcinoma	No additive Hyperglycosylated hCG β-subunit 20 ng/ml Hyperglycosylated hCG ß-subunit 200 ng/m	100% cell count after 24 h 115% cell count after 24 h 142% cell count after 24 h	P=0.008

germ cell testicular cancer, Hec-1-a endometrial carcinoma, ScaBER squamous bladder carcinoma, KLE endometrial adenocarcinoma, SK-MES-1 epithelial lung carcinoma, KM-H2 Hodgkin's lymphoma, T24 epithelial bladder carcinoma, and CasKi epithelial cervical carcinoma cell line. In all ten of 10 cell lines hyperglycosylated hCG and its ß-subunit promoted cancer cell growth or promoted malignancy (Table **5**) [1-4].

I concluded, considering my results and the 7 other independent investigator's results (Table **4**) that hyperglycosylated hCG and its ß-subunit produced by cancer cells seemingly promoted cancer malignancy, promoting cell growth, promoting cell-cell invasion and blocking cell apoptosis. No investigator, neither myself nor the 7 independent investigators [1-12], had seen a cancer that did not respond to hyperglycosylated hCG or ß-subunit, thus I say that hyperglycosylated hCG and its ß-subunit drives malignancy in all or most cancers.

5. HYPERGLYCOSYLATED hCG AND ITS ß-SUBUNIT DRIVES MALIGNANCY IN ALL OR MOST HUMAN CANCERS

I needed to justify my statement that hyperglycosylated hCG and its ß-subunit drives malignancy in all or most human cancers. How many cancers had I tested?

Table **6** list common cancer types or histologies. It lists 88 cancers and excludes a few very rare cancers. As shown (Table **1** and **6**), I had detected the hCG forms produced in 58 of the 88 cancer types (66%). Either I or the 7 independent research centers had demonstrated that the patient cells or a cell line responded to hyperglycosylated hCG or ß-subunit produced by the cancer cell in a malignant manner (promotes growth, promotes invasion or blocks apoptosis) in 16 of 88 (18%) cancers (Table **6**). Based on this, and on the fact that everybody has been looking and no one has seen to date a cancer that does not respond to these molecules, I make the claim that hyperglycosylated hCG (trophoblastic cancers) and its ß-subunit (non-trophoblastic or other cancers) promotes malignancy in all or most human cancers.

Upon reflection, hyperglycosylated hCG and its ß-subunit could be secondary molecules to another molecule, the primary molecule, which controls cancer cell malignancy. It could just be incidental that we show hyperglycosylated hCG and its ß-subunit binding a TGF-ß receptor controlling malignancy. To test this possibility, we used a specific antibody, B152, that only binds hyperglycosylated hCG and its ß-subunit to precipitate and inactivate their action.

As shown in Table **7**, using seven different cancer cell lines, B152 at a concentration of 2.0 µg/ml, completely blocked cell growth or blocked malignancy, returning cells to the concentration before growth started or 70% confluency level. Whatever B152 blocks, hyperglycosylated hCG and its ß-subunit, must be the primary molecule blocking malignancy. This shows that hyperglycosylated hCG and its ß-subunit must be the primary malignancy molecule, since their blockage returned the cells to starting growth level.

Figure **3** show a second experiment designed to confirm the hypothesis. Human choriocarcinoma cells were transplanted under the skin of 8 nude mice. Two weeks later the appearance of metastasis showed that the cancer was established in nude mice. Four mice were given antibody B152 twice weekly and 4 mice were given non-specific mouse immunoglobulin G (IgG) twice weekly. As shown in Figure **3**, B152 blocked out malignancy bring the cancer to a benign or oncostasis status, IgG did not block malignancy.

This shows that B152 completely blocks out malignancy by specifically precipitating hCG and its ß-subunit, confirming that hyperglycosylated hCG or its ß-subunit specifically (as primaries) drives malignancy.

This manuscript proves that hyperglycosylated hCG (trophoblastic cancers) and its ß-subunit (non-trophoblastic or other cancers) drives all or most human malignancies. Since it is confirmed by 7 independent laboratories in independent studies it must be considered as proven.

6. DISCUSSION

Finding what molecules control malignancy in human cancer should lead to a massive change in human cancer research. Not just because hyperglycosylated hCG and its ß-subunit drives malignancy in cancer, but because without malignancy a cancer is not a cancer. As such, without hyperglycosylated hCG and its free ß-subunit a cancer is not a cancer. Thus, hyperglycosylated hCG and its ß-subunit drives all or most human cancers.

Research with hyperglycosylated hCG and its ß-subunit should be considerable following publication of this article. Not just with other research centers testing, expanding-on and developing further what is known

Table 6: Cancer Sites Tested as a Tumor Marker, all Common Malignancies Listed, a Few Rare Cancers are Not Included

Organ	Histology	Tumor Marker	Test for malignancy (growth, invasion, apoptosis)
Bladder	Adenocarcinoma	Tested	Cell line responds to hyperglycosylated hCGß
Bladder	Small cell carcinoma	Tested	Cell line responds to hyperglycosylated hCGß
Bladder	Squamous cell carcinoma	Tested	Cell line responds to hyperglycosylated hCGß
Blood	Myelogenous leukemia	Not tested	
Blood	Myelogenous leukemia	Not tested	
Blood	Lymphocytic leukemia	Not tested	
Blood	Hodgkin's lymphoma	Tested	Cell line responds to hyperglycosylated hCGß
Blood	Non-Hodgkin's lymphoma	Tested	
Brain	Craniopharyngiomas	Not tested	
Brain	Glioblastoma	Not tested	
Brain	Haemangioblastoma	Not tested	
Brain	Meningiomas	Not tested	
Brain	Medulloblastoma	Not tested	
Breast	Inflammatory Breast Cancer	Tested	
Breast	Ductal Carcinoma	Tested	
Breast	Tubular Carcinoma	Tested	
Breast	Medullary Carcinoma	Tested	
Breast	Mucinous Carcinoma	Tested	
Breast	Papillary Carcinoma	Tested	
Breast	Cribriform Carcinoma	Tested	
Breast	Lobular Carcinoma	Tested	
Cervical	Squamous cell carcinomas	Tested	Tissue responds to hyperglycosylated hCGß
Cervical	Adenocarcinomas	Tested	
Cervical	Adenosquamous carcinomas	Tested	
Colorectal	Adenocarcinoma	Tested	Cell line responds to hyperglycosylated hCGß
			Tissue responds to hyperglycosylated hCGß
Colorectal	Gastrointestinal carcinoid	Tested	
Duodenum	Adenocarcinoma	Not tested	
Ear	Basal skin carcinoma	Not tested	
Endometrial	Endometrioid	Tested	Tissue responds to hyperglycosylated hCGß
Endometrial	Mucinous	Tested	
Endometrial	Serous	Tested	Cell line responds to hyperglycosylated hCGß
Endometrial	Adenocarcinoma	Tested	Cell line responds to hyperglycosylated hCGß
Eye	Intraocular melanoma	Not tested	
Eye	Intraocular lymphoma	Not tested	
Gastric	Adenocarcinoma	Tested	
Hepatic	Hepatocellular carcinoma	Tested	
Hepatic	Cholangiocarcinoma	Tested	
Hepatic	Hepatoblastoma	Tested	
Intestine	Adenocarcinoma	Tested	

(Table 6). Continued.

Organ	Histology	Tumor Marker	Test for malignancy (growth, invasion, apoptosis)
Intestine	Sarcoma	Tested	
Intestine	Carcinoid	Tested	
Lung	Small cell	Tested	Cell line responds to hyperglycosylated hCGß
Lung	Non-small cell	Tested	
Lung	Carcinoid	Tested	
Muscle	Rhabdomyosarcoma	Not tested	
Ovarian	Serous cystadenocarcinoma	Tested	Tissue responds to hyperglycosylated hCGß
			Cell line responds to hyperglycosylated hCGß
Ovarian	Adenocarcinoma	Tested	
Ovarian	Endometrioid tumor	Tested	
Ovarian	Mucinous cystadenocarcinoma	Tested	
Ovarian	Mucinous adenocarcinoma	Tested	
Ovarian	Mullerian tumor	Tested	
Ovarian	Dysgerminoma	Tested	
Ovarian	Endodermal sinus	Tested	
Ovarian	Teratoma	Tested	
Ovarian	Yolk sac	Tested	
Ovarian	Choriocarcinoma	Tested	Cell line responds to hyperglycosylated hCGß
Parathyroid	Adenoma	Not tested	
Pituitary	Carcinoma	Not tested	
Pancreatic	Adenocarcinoma	Tested	
Pancreatic	Acinar squamous carcinoma	Tested	
Pancreatic	Colloid carcinoma	Tested	
Pancreatic	Intraductal papillary mucinous	Tested	
Placental	Choriocarcinoma	Tested	
Prostate	Adenocarcinoma	Not tested	Cell line responds to hyperglycosylated hCGß
Renal	Clear cell carcinoma	Tested	
Renal	Papillary carcinoma	Tested	
Renal	Chromophobe carcinoma	Tested	
Renal	Transitional cell carcinoma	Tested	
Skin	Basal cell carcinoma	Not tested	
Skin	Squamous cell	Not tested	
Skin	Melanoma	Not tested	
Testicular	Seminoma	Not tested	
Testicular	Spermatocytic seminoma	Not tested	
Testicular	Embryonal	Tested	
Testicular	Yolk sac	Tested	
Testicular	Choriocarcinoma	Tested	Cell line responds to hyperglycosylated hCGß
Testicular	Teratoma	Tested	
Throat	Hypopharyngeal	Not tested	
Throat	Laryngeal	Not tested	

(Table 6). Continued.

Organ	Histology	Tumor Marker	Test for malignancy (growth, invasion, apoptosis)
Throat	Laryngopharyngeal	Not tested	
Throat	Nasopharyngeal	Not tested	
Throat	Pharyngeal	Not tested	
Throat	Oropharyngeal	Not tested	
Uterine	Sarcoma	Tested	Tissue responds to hyperglycosylated hCGß
Vulvar	Squamous cell	Tested	
Vulvar	Adenocarcinoma	Tested	
Thyroid	Medullary thyroid carcinoma	Not tested	
Thyroid	Papillary	Not tested	
Thyroid	Oxyphil cell carcinoma	Not tested	

Table 7: Cancer cells cultured to 70% flask confluency (confl), then cultured 24 h with hyperglycosylated hCG (hCG-H), or 24 h with antibody B152 in quadruplicate and cells counted. hCG-H is hyperglycosylated hCG and hCG-H-ß is hyperglycosylated hCG ß-subunit, and B152 is antibody B152. Values are percent change from 70% confl. Inherant changes following 0 pmol/ml or 0 µg/ml incubations due to hyperglycosylated hCG or ß-subunit produced by cells

70% confl	hCG-H 0 pmol/ml	hCG-H 10 pmol/ml	hCG-H 100 pmol/ml	B152 0 µg/ml	B152 0.5 µg/ml	B152 1.0 µg/ml	B152 2.0 µg/ml
A. Trophoblastic malignancies							
JAr choriocarcinoma cell line, 70% confl = 334,500 ± 33,000 cells							
100 ± 10%	128 ± 8.4%	149 ± 18%	183 ±10%	128 ± 8.4%	110 ± 23%	105 ± 15%	101 ± 0.9%
JEG-3 choriocarcinoma cell line, 70% confl = 430,000 ± 33,110 cells							
100 ± 7.7%	123 ± 11%	145 ± 8.5%	164 ± 16%	123 ± 11%	115 ± 7.6%	103 ±2.4%	101 ± 8.1%
NTERA testicular germ cell malignancy, 70% confl = 391,000 ± 10,160 cells							
100 ± 2.6%	114 ± 19%	130 ± 10%	168 ± 12%	114 ± 19%	119 ± 10%	117± 2.4%	100 ± 0.7%
70% confl	hCG-H-ß 0 pmol/ml	hCG-H-ß 10 pmol/ml	hCG-H-ß 100 pmol/ml	B152 0 µg/ml	B152 0.5 µg/ml	B152 1.0 µg/ml	B152 2.0 µg/ml
B. Non-trophoblastic malignancies							
SCaBER bladder epithelial carcinoma cells, 70% confl = 334,000 ± 17,000 cells							
100 ± 5.1%	147 ± 2.0%	169 ± 12%	193 ± 3.7%	147 ± 2.0%	129 ± 16%	120 ± 3.7%	100 ± 2.9%
T24 bladder epithelial carcinoma cells, 70% confl = 559,000 ± 24,000 cells							
100 ± 4.2%	120 ± 4.4%	162 ± 2.6%	172 ± 5.4%	120 ± 4.4%	114 ± 12%	103 ± 1.1%	100 ± 3.5%
Hec-1-a endometrial carcinoma cells, 70% confl = 390,500 ± 12,800 cells							
100 ± 3.3%	140 ± 11%	169 ± 5.6%	171 ± 7.2%	140 ± 11%	128 ± 7.7%	132 ± 8.2%	103 ± 3.1%
KLE endometrial adenocarcinoma cells, 70% confl = 331,000 ± 6,950 cells							
± 2.1%	182 ± 16%	222 ± 1.7%	242 ± 2.8%	182 ± 16%	142 ± 1.3%	118 ± 3.3%	102 ± 2.5%

about hyperglycosylated hCG and its ß-subunit and cancer. But with laboratories finding antibodies to, and processes that activate and block hyperglycosylated hCG and its ß-subunit generation in cancers. With this research should come possible cures to cancer and means for people to block any chance of developing cancer.

If you claim that hyperglycosylated hCG and its ß-subunit drives all or most human cancers, one might say that hyperglycosylated hCG and its ß-subunit causes cancer. As shown hyperglycosylated hCG and its ß-subunit drive blastocyst implantation in pregnancy [33-35] and hemochorial placentation deep implantation in pregnancy [36,37].

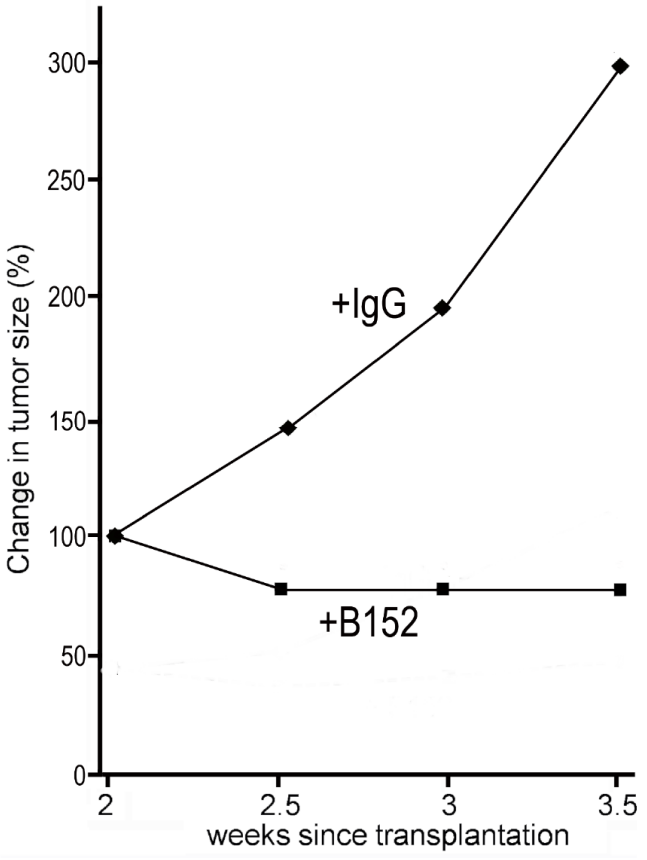

Figure 3: Nude mice were transplanted with human choriocarcinoma, Once malignancy metastases detected, 4 nude mice were given B152 and 4 given a non-specific IgG. B152 halted malignancy in cancer creates a benign status of oncostasis.

Hyperglycosylated hCG action in pregnancy implantation is followed by a much larger concentration of the hormone hCG in pregnancy, this blankets or blocks the actions of hyperglycosylated hCG, or neutralizes the use of hyperglycosylated hCG, a cancer-causing agent, in pregnancy [38]. Hyperglycosylated hCG runs out of control or not blocked by hCG in cancer cases.

I have proposed in papers on blastocyst implantation, after showing that hyperglycosylated hCG and is ß-subunit drives implantation, and that failures of implantation causes spontaneous abortion and biochemical pregnancies, 40% pregnancy failures, I propose that women should receive a shot of hyperglycosylated hCG before achieving pregnancy to prevent pregnancy failures [33,34]. Considering what we now know, that hyperglycosylated hCG and its ß-subunit drives and causes all or most human cancers, I withdraw this statement. Hyperglycosylated hCG, a cancer causing or driving agent, may be too dangerous to use in pregnancy.

I finish by stating that if hyperglycosylated hCG and its ß-subunit drives and causes cancer, the statement that hyperglycosylated hCG = cancer, maybe correct.

REFERENCES

[1] Cole LA. Hyperglycosylated hcg and its free ß-subunit: the root causes of malignancy and cancer. J Molec Oncol Res 2017; 1: 53-63.

[2] Cole LA. Hyperglycosylated hcg drives malignancy in most or all human cancers: tying all research together. J Analyt Oncol 2018; 7: 14-21. https://doi.org/10.6000/1927-7229.2018.07.01.3

[3] Cole LA, Butler SA. Cole LA, Butler SA. B152 anti-hyperglycosylated human chorionic gonadotropin free β-Subunit. A new, possible treatment for cancer. J Reprod Med 2015; 60: 13-20.

[4] Cole LA, Butler SA. Hyperglycosylated hCG, hCGß and Hyperglycosylated hCGß: Interchangeable Cancer Promoters. Molec Cellul Endcrinol 2012; 349: 232-238. https://doi.org/10.1016/j.mce.2011.10.029

[5] Gillott DJ, Iles RK, Chard T. The effects of beta-human chorionic gonadotrophin on the *in vitro* growth of bladder cancer cell lines. Br J Cancer 1996; 73: 323-326. https://doi.org/10.1038/bjc.1996.56

[6] Butler SA, Ikram MS, Mathieu S. The increase in bladder carcinoma cell population induced by the free beta subunit of hCG is a result of an anti-apoptosis effect and not cell proliferation. Brit J Cancer 2000; 82: 1553-1556.

[7] Devi GR, Oldenkamp JR, London CA, Iversen PL. Inhibition of human chorionic ß-subunit modulates the mitogenetic effect of *c-myc* in human prostate cancer cells. Prostate 2002; 53: 200-310. https://doi.org/10.1002/pros.10151

[8] Cole LA, Cole LA, Dai D, Leslie KK, Butler SA, Kohorn EI. Gestational trophoblastic diseases: 1. Pathophysiology of hyperglycosylated hCG-regulated neoplasia. Gynecologic Oncology 2006; 102: 144-149.

[9] Jankowska A, Gunderson SI, Warchol JB. Reduction of hCGß subunit expression by modified U1 snRNA caused apoptosis in cervical cancer cells. Molec Cancer 2008; 7: 26-29. https://doi.org/10.1186/1476-4598-7-26

[10] Li D, Wen X, Ghali L, *et al*. hCG β expression by cervical squamous carcinoma-*in vivo* histological association with tumour invasion and apoptosis. Histopathol 2008; 53: 147-55. https://doi.org/10.1111/j.1365-2559.2008.03082.x

[11] Guo X, Liu G, Schauer IG, *et al*. Overexpression of the β Subunit of Human Chorionic Gonadotropin Promotes the Transformation of Human Ovarian Epithelial Cells and Ovarian Tumorigenesis. Am J Pathol 2011; 179: 1385-1393. https://doi.org/10.1016/j.ajpath.2011.05.018

[12] Kawamata F, Nishihara H, Homma S, *et al*. Chorionic gonadotropin-ß modulates epithelial-mesenchymal transition in colorectal carcinoma metastasis. Am J Path 2018; 188: 207-215. https://doi.org/10.1016/j.ajpath.2017.08.034

[13] Lustbader JW, Yarmush DL, Birken S. Puett D, Canfield R. The application of chemical studies of human chorionic gonadotropin to visualize is three-dimensional structure. Endocr Rev 2013; 14: 291-310.

[14] Wu H, Lusbader JW, Yee L, Canfield RE, Hendriickson WA. Structure of human chorionic gonadotropin at 2.6Å resolution from MAD analysis of the selenmethionyl protein. Structure 1994; 2: 545-558. https://doi.org/10.1016/S0969-2126(00)00054-X

[15] Lapthorn AJ, Harris DC, Littlejohn A, Lustbader JW, Canfield RE, Machin KJ, Morgan FJ, Isaacs NW. Crystal structure of human chorionic gonadotropin. Nature 1994; 369: 455-462. https://doi.org/10.1038/369455a0

[16] Cole LA. The Minute Structural Difference Between the Hormone hCG and the Autocrine Hyperglycosylated hCG. J Glycobiol 2017; 6: 1000127. https://doi.org/10.4172/2168-958X.1000127

[17] Berndt S, Blacher S, Munuat C, Detilleux J, Evain-Brion D, Noel A, Fournier T, Foidart JM. Hyperglycosylated human chorionic gonadotropin stimulates angiogenesis through TGF-ß receptor activation. FASEB J 2013; 12-213686.

[18] Ahmud F, Ghosh S, Sinha S, Joshi SD, Mehta VS, Sen E. TGF-ß-induced hCG-ß regulates redox homeostasis in glioma cells, Molec Cellul Biochem 2015; 399: 105-112. https://doi.org/10.1007/s11010-014-2237-6

[19] Rao CV. 15 - Paradigm shift on the targets of hCG actions. In: Human Chorionic Gonadotropin (hCG) (Second Edition) Cole LA, Butler SA (Eds), 2015; pp. 141-147. https://doi.org/10.1016/B978-0-12-800749-5.00015-8

[20] Isaacs NW. Cystine knots. Current Opinion in Struct Biol 1995; 5: 391-395. https://doi.org/10.1016/0959-440X(95)80102-2

[21] Beebe JS, Huth JR, Ruddon RW, Combination of the chorionic gonadotropin free beta-subunit with alpha. Endocrinol 1990; 126: 384-391. https://doi.org/10.1210/endo-126-1-384

[22] Golde DW, Schambelan M, Weintraub BD, Rosen SW. Gonadotropin-secreting renal carcinoma. Cancer 1974; 33: 1048-1053. https://doi.org/10.1002/1097-0142(197404)33:4<1048::AID-CNCR2820330423>3.0.CO;2-A

[23] Fukayama M, Hayashi Y, Koike M. Human chorionic gonadotropin in gastric carcinoma. Virchows Archiv 1987; 411: 205-212. https://doi.org/10.1007/BF00735025

[24] Braunstein GD, Vogel CL, Vaitukaitis JL, Ross GT. Ectopic production of human chorionic gonadotropin in Ugandam patients with hepatocellular carcinoma. Cancer 1973; 32: 223-226. https://doi.org/10.1002/1097-0142(197307)32:1<223::AID-CNCR2820320133>3.0.CO;2-A

[25] Kahn CR, Rosen SW, Weintraub BD, Fajans SS, Gorden P. Ectopic production of chorionic gonadotropin and its subunits by islet-cell tumors-a specific marker for malignancy. New Engl J Med 1977; 297: 565-569. https://doi.org/10.1056/NEJM197709152971101

[26] Hussain F. Gynecologic tumor markers: Tumor marker overview. MedScape https://emedicine.medscapecom/article/269839-overview.

[27] Sisinni L, Landriscina M. The role of human chorionic gonadotropin as a tumor marker: Biochemical and clinical aspects. Adv Exp Med Biol 2015; 897: 159-176. https://doi.org/10.1007/978-94-017-7215-0_11

[28] Pappapetrou PD, Sakarelou NP, Braouzi H, Fessas Ph. Ectopic production of human chorionic gonadotropin (hCG) by neoplasms: The value of measurements of immunoreactive hCG in the urine as a screening procedure. Cancer 1980; 45: 2583-2592. https://doi.org/10.1002/1097-0142(19800515)45:10<2583::AID-CNCR2820451018>3.0.CO;2-W

[29] Acevedo HF, Krichevsky A, Campbell-Acevedo EA, Galyon JC, Buffo MJ, Hartsock RJ. Flow cytometry method for the analysis of membrane-associated human chorionic gonadotropin, its subunits, and fragments on human cancer cells. Cancer 1992; 69: 1818-1828. https://doi.org/10.1002/1097-0142(19920401)69:7<1818::AID-CNCR2820690726>3.0.CO;2-7

[30] Regelson W. Have we found the "definitive cancer biomarker"? The diagnostic and therapeutic implications of human chorionic gonadotropin-beta statement as a key to malignancy. Cancer 1995; 76: 1299-1301. https://doi.org/10.1002/1097-0142(19951015)76:8<1299::AID-CNCR2820760802>3.0.CO;2-L

[31] Cole LA, Tanaka A, Kim GS, Park S-Y, Koh MW, Schwartz PE, Chambers JT, Nam J-H. Beta core fragment (β-core / UGF / UGP), a tumor marker: Seven year report. Gynecol Oncol 1996; 60: 264-270. https://doi.org/10.1006/gyno.1996.0036

[32] Cole LA. The O-linked oligosaccharides are strikingly different on pregnancy and choriocarcinoma hCG. J Clin Endocrinol Metab 1987; 65: 811-813. https://doi.org/10.1210/jcem-65-4-811

[33] Sasaki Y, Ladner DG, Cole LA. Hyperglycosylated hCG the source of pregnancy failures. Fertil Steril 2008; 89: 1871-1786. https://doi.org/10.1016/j.fertnstert.2007.03.010

[34] Cole LA. Hyperglycosylated hCG and pregnancy failures. J Reprod Immunol 2012; 93: 119-122. https://doi.org/10.1016/j.jri.2012.01.001

[35] Evans J. Hyperglycosylated hCG: a Unique Human Implantation and Invasion Factor. Am J Reprod Immunol 2016; 75: 333-340. https://doi.org/10.1111/aji.12459

[36] Cole LA, Brennan MC, Hsu C-D, Bahado-Singh R, Kingston JM. Hyperglycosylated hCG Drives Deep Implantation in Pregnancy Causing Preeclampsia and Gestational Hypertension. In: Human Chorionic Gonadotropin (hCG) Version 3, Ed: Cole LA, Butler SA. Elsevier 2018.

[37] Bahado-Singh RO, Oz AU, Kingston JM, Shahabi S, Hsu CD, Cole LA. The role of hyperglycosylated hCG in trophoblast invasion and the prediction of subsequent pre-eclampsia. Prenat Diagn 2002; 22: 478-481. https://doi.org/10.1002/pd.329

[38] Cole LA. hCG attenuates hyperglycosylated hCG-driven growth and invasion. J Molec Oncol Res 2018; 2: 13-20.

Received on 11-04-2018 Accepted on 20-04-2018 Published on 26-07-2018

https://doi.org/10.6000/1927-7229.2018.07.03.4