Bari,
7-10 novembre 2013

12° Congresso Nazionale AME
Associazione Medici Endocrinologi

6th Joint Meeting with AACE
American Association of Clinical Endocrinologists

Bari, 7-10 novembre 2013

Terapie endocrino-metaboliche e rischio oncologico

GH

Marco Gallo
SCDU Endocrinologia Oncologica
AO Città della Salute e della Scienza di Torino
Molinette - COES

Does growth hormone cause cancer?

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7-10 novembre 2013

- physiology/pathophysiology
- in vitro studies
- animal studies
- epidemiologic studies
- GH excess clinical settings
  - acromegaly
  - unlicensed GH therapy w/o GHD
- GH replacement in GHD

Jenkins PJ et al.; *Clin Endocrinol* 2006

GH/IGF-1 axis & tumors

Bari,
7-10 novembre 2013

endocrine, autocrine, and paracrine actions

- influencing factors:
  - IGF-1 receptor (type 1) density
  - IGF-1/insulin receptor hybrids

Jenkins PJ et al.; *Clin Endocrinol* 2006

GH/IGF-1 axis & tumors

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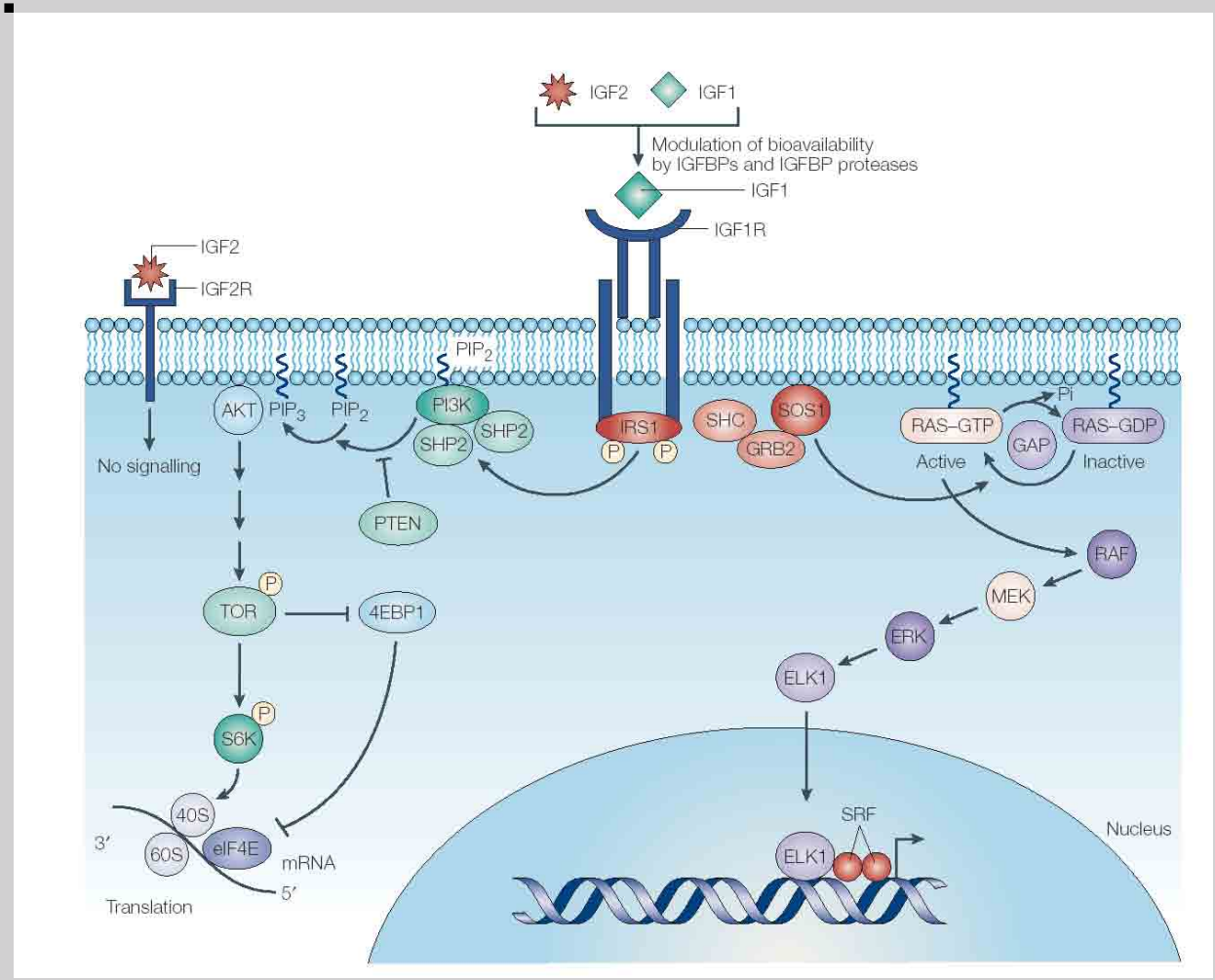
7-10 novembre 2013



Pollak MN et al.; *Nat Rev Cancer* 2004

IGF-1 and insulin receptors

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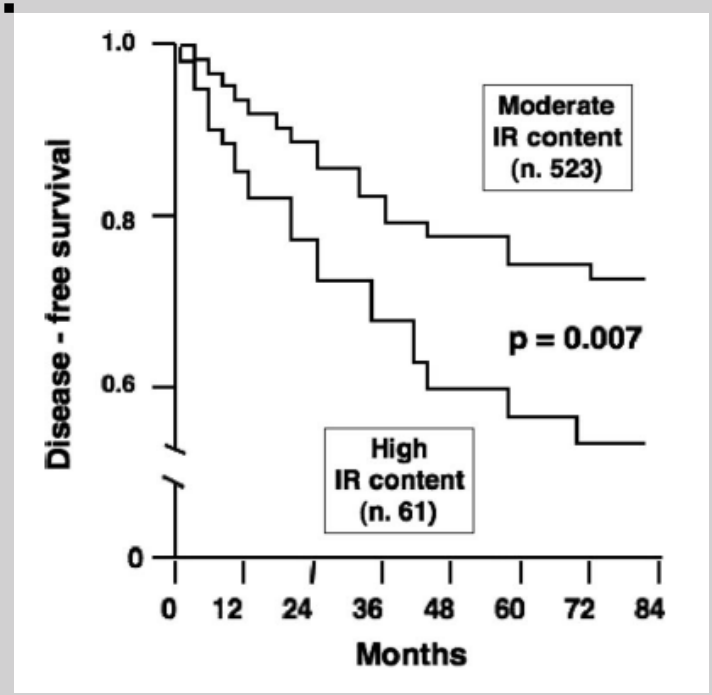
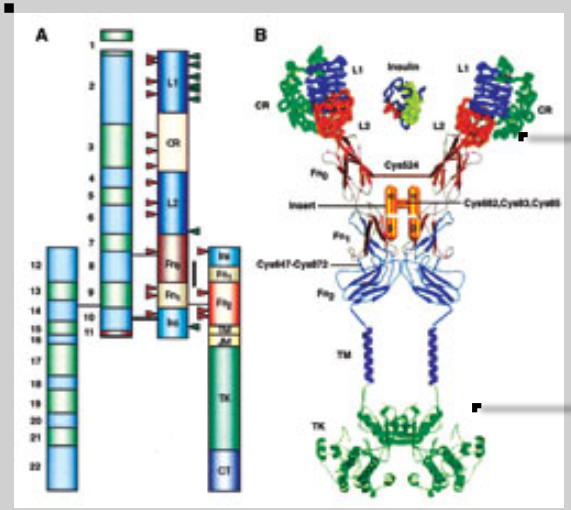


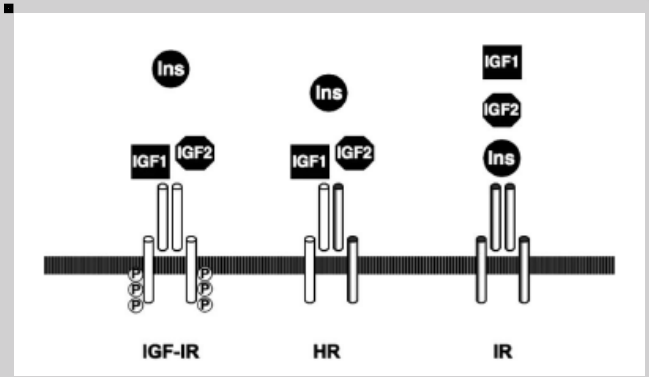
Mathieu MC et al; *Proc Assoc Am Physicians*. 1997

homology between IR & IGF-IR

45-65%



60-85%



Frasca F et al.; *Arch Physiol Bioch* 2008

GH/IGF-1 axis & tumors

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endocrine, autocrine, and paracrine actions

- influencing factors:
  - IGF-1 receptor (type 1) density
  - IGF-1/insulin receptor hybrids
  - IGF-binding proteins (IGFBP-3, IGFBP-2)
    - regulation of free IGF-1 amount
    - IGF-1-independent actions
  - polymorphisms (IGF-1 gene/GH synthesis pathway)
  - proteases (e.g. PSA), tissue architecture, etc.

Jenkins PJ et al.; *Clin Endocrinol* 2006
Banerjee I & Clayton PE, *Endocrinol Metab Clin N Am* 2007

GH/IGF-1 axis & tumors

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powerful effects of IGF-1 on:

- cellular proliferation
- apoptosis

= increased epithelial turnover

across the general population, serum IGF-I levels vary between individuals, and it is postulated that this may impact upon cancer risk

GH/IGF-1 axis & tumors

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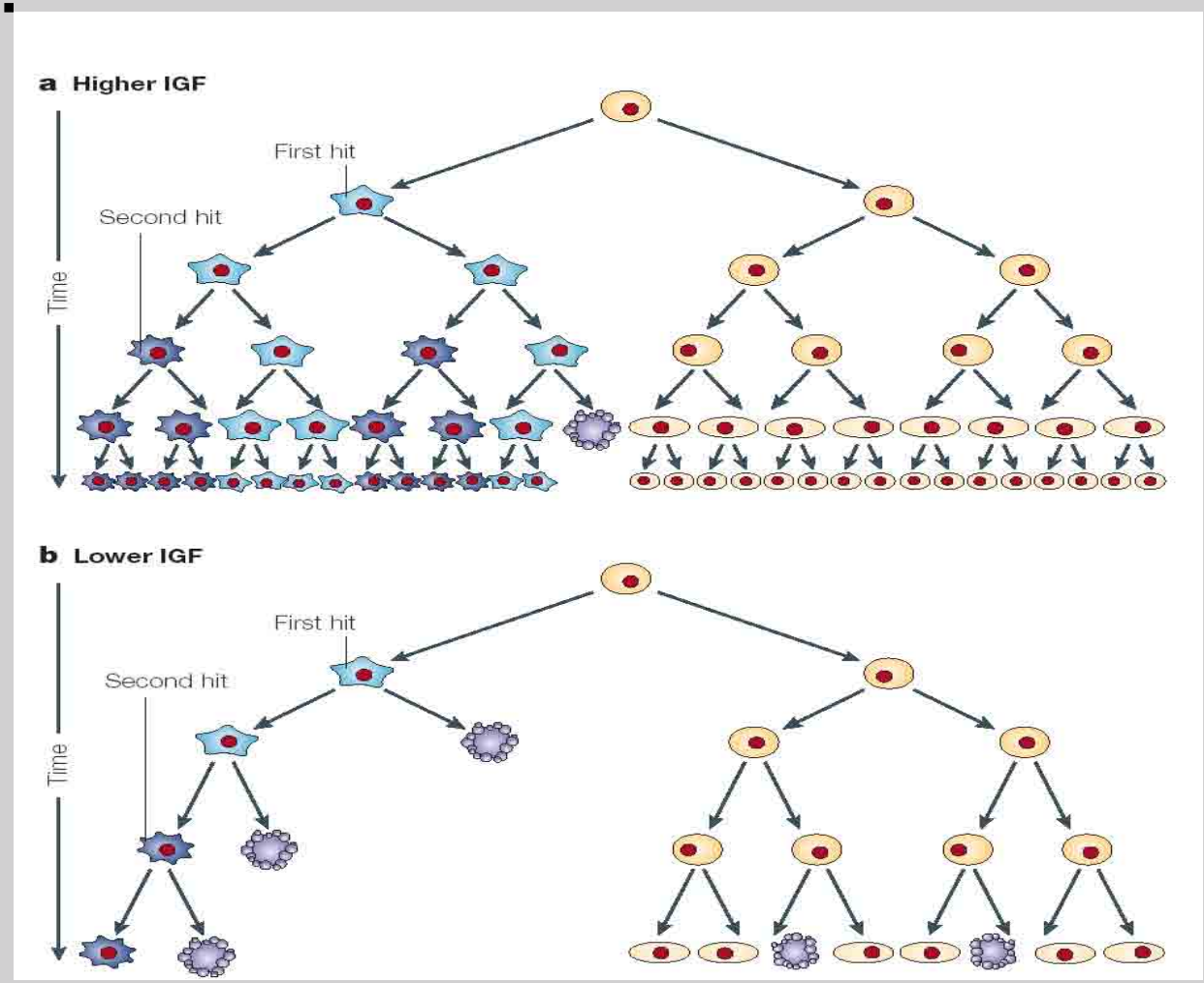

Pollak MN et al.; *Nat Rev Cancer* 2004

GH/IGF-1 axis & tumors

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powerful effects of IGF-1 on:

- cellular proliferation
- apoptosis
- angiogenesis & lymphangiogenesis
- cell motility
- metastases
- development of resistance to chemotherapeutics

Jenkins PJ et al.; *Clin Endocrinol* 2006
Pekic S & Popovic V, *Eur J Endocrinology* 2013

GH/IGF-1 axis & tumors
animal studies

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- transfected/silenced mice

Bates P et al.; *Br J Cancer* 1995
Yang XF et al., *Cancer Res* 1996

- Ab against IGF-1R

Arteaga CL et al.; *J Clin Invest* 1989

- selective knockout of hepatic IGF-1 gene

Wu Y et al.; *Cancer Res 2002*
Wu Y et al.; *Cancer Res 2003*

large IGF-1 level variations vs. physiology

GH/IGF-1 axis & tumors
epidemiological studies

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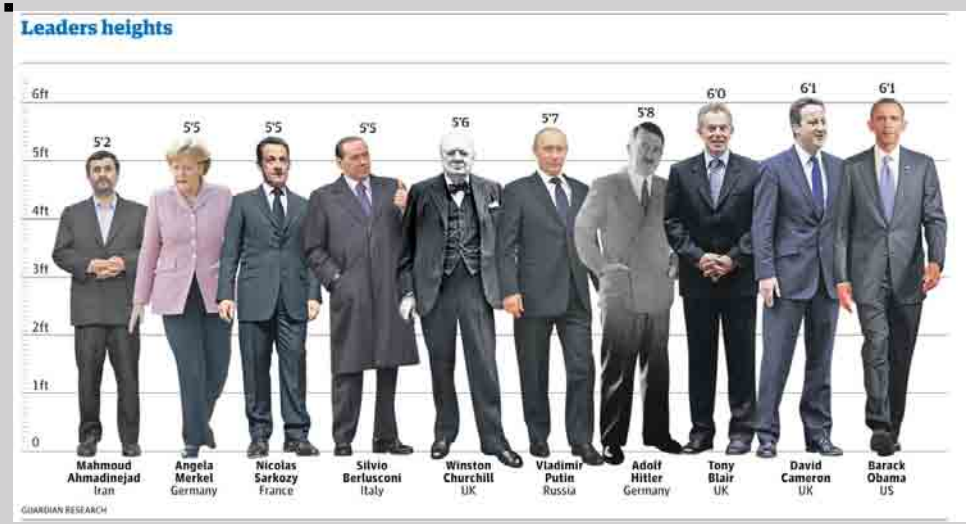
- childhood growth data would predict malignancy in later life
- birth weight/stature
- peak height velocity (& breast cancer)
- final height (& breast, prostate, and CR cancer)
- leg lenght



GH/IGF-1 axis & tumors
epidemiological studies

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general population

- possible link between GH/IGF-1 levels & the development of a variety of different cancers
- subjects with IGF-1 levels that are in the higher centiles of the normal range would have a significantly increased risk of developing
  - breast, prostate, and colon cancer
  - lung cancer?

Hankinson SE et al.; *Lancet* 1998
Wolk A et al., *J Natl Cancer Inst* 1998

Height and cancer incidence in the Million Women Study: prospective cohort, and meta-analysis of prospective studies of height and total cancer risk

Lancet Oncol 2011; 12: 785–94

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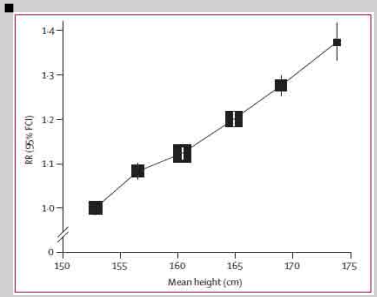
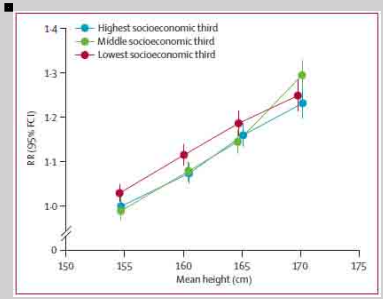
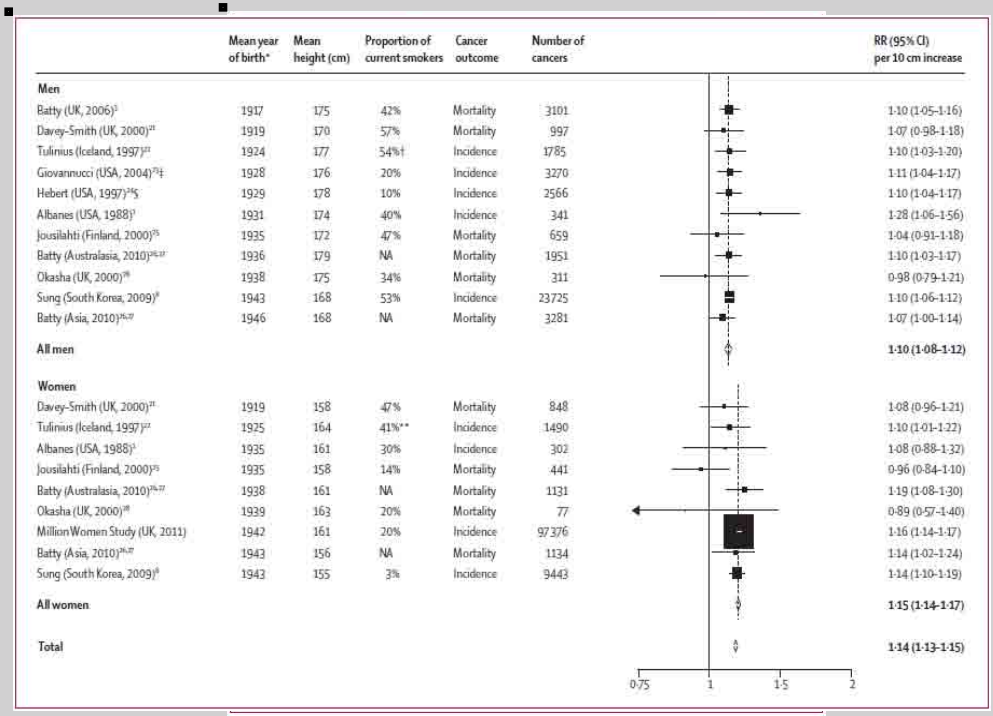
taller people are at increased risk of cancer

- large prospective cohort of ~1.3 M middle-aged women w/o previous cancer (follow-up 9.4 yy)
- ~97,000 incident cancers (17 sites)
- RR for total cancer **for every 10 cm increase in height** was
  1.16 (95% CI 1·14–1·17; p<0·0001)
- statistically significant increased risk for 10 sites
  - independently of socioeconomic status & geographic area
  - lower in current smokers
- IGF-1 levels in childhood/adulthood?







	Mean year of birth*	Mean height (cm)	Proportion of current smokers	Cancer outcome	Number of cancers	RR (95% CI) per 10 cm increase
Men						
Batty (UK, 2006)[5]	1917	175	42%	Mortality	3101	1·10 (1·05–1·16)
Davey-Smith (UK, 2000)[21]	1919	170	57%	Mortality	997	1·07 (0·98–1·18)
Tulinius (Iceland, 1997)[22]	1924	177	54%†	Incidence	1785	1·10 (1·03–1·20)
Giovannucci (USA, 2004)[23]‡	1928	176	20%	Incidence	3270	1·11 (1·04–1·17)
Hebert (USA, 1997)[24]§	1929	178	10%	Incidence	2566	1·10 (1·04–1·17)
Albanes (USA, 1988)[3]	1931	174	40%	Incidence	341	1·28 (1·06–1·56)
Jousilahti (Finland, 2000)[25]	1935	172	47%	Mortality	659	1·04 (0·91–1·18)
Batty (Australasia, 2010)[26,27]	1936	179	NA	Mortality	1951	1·10 (1·03–1·17)
Okasha (UK, 2000)[28]	1938	175	34%	Mortality	311	0·98 (0·79–1·21)
Sung (South Korea, 2009)[8]	1943	168	53%	Incidence	23725	1·10 (1·06–1·12)
Batty (Asia, 2010)[26,27]	1946	168	NA	Mortality	3281	1·07 (1·00–1·14)
All men						**1·10 (1·08–1·12)**
Women						
Davey-Smith (UK, 2000)[21]	1919	158	47%	Mortality	848	1·08 (0·96–1·21)
Tulinius (Iceland, 1997)[22]	1925	164	41%**	Incidence	1490	1·10 (1·01–1·22)
Albanes (USA, 1988)[3]	1935	161	30%	Incidence	302	1·08 (0·88–1·32)
Jousilahti (Finland, 2000)[25]	1935	158	14%	Mortality	441	0·96 (0·84–1·10)
Batty (Australasia, 2010)[26,27]	1938	161	NA	Mortality	1131	1·19 (1·08–1·30)
Okasha (UK, 2000)[28]	1939	163	20%	Mortality	77	0·89 (0·57–1·40)
Million Women Study (UK, 2011)	1942	161	20%	Incidence	97376	1·16 (1·14–1·17)
Batty (Asia, 2010)[26,27]	1943	156	NA	Mortality	1134	1·14 (1·02–1·24)
Sung (South Korea, 2009)[8]	1943	155	3%	Incidence	9443	1·14 (1·10–1·19)
All women						**1·15 (1·14–1·17)**
Total						**1·14 (1·13–1·15)**

Green J et al., Lancet Oncol 2011

GH/IGF-1 axis & tumors
acromegaly

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increased risk of:

- colorectal tumors: 2-7.6x
- thyroid tumors
- breast tumors? prostate cancer?

- ✓ genetics?
- ✓ hyperinsulinemia & diabetes role?

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Best Practice & Research Clinical Endocrinology & Metabolism
Vol. 22, No. 4, pp. 639–657, 2008
doi:10.1016/j.beem.2008.08.011
available online at http://www.sciencedirect.com

Andrew G. Renehan* PhD, FRCS
Bernadette M. Brennan MD, FRCPCH

Acromegaly, growth hormone and cancer risk

Table 1. Colonoscopy studies in acromegalic patients.

	Country	Case/control	Mean age—acromegaly	Adenoma prevalence		Comments on controls	Conclusions—prevalence rate
				Acromegaly	Controls		
Klein et al, 1982	USA	17/–	49	5 (29)	–	Two literature review papers	Increased
Ituarte et al, 1984	USA	12/–	56	2 (15)	–	Population cancer rates only	Increased
Brunner et al, 1990	USA	29/–	NR	4 (14)	–	Population cancer rates only	Increased
Ezzat et al, 1991	USA	23	47	8 (35)	–	One study from literature	Increased
Ortego et al, 1994	Spain	27/–	49	7 (26)	–	Compared with literature	Inclusive
Ladas et al, 1994	Greece	54/–	47	5 (9)	–	Compared with literature	No increase
Vasen et al, 1994	NH	49	54	11 (22)	–	Compared with literature	Increased
Delhougne et al, 1995	France	103/138	51	23 (22)	11 (8)	In-house non-acromegalic patients with IBS symptoms	Increased
Jenkins et al, 1997	UK	127/562	22–80	34 (26)	63 (11)	In-house non-acromegalic symptomatic patients	Increased
Renehan et al, 2000	UK	115/models	55	14 (12)	Age-dependent ranges	Controls modelled from 8 autopsy ($n = 3559$) and 4 screening colonoscopy ($n = 810$) studies	No increase
Martino et al, 2004	Italy	75/75	54	3 (10)	1 (10)	Age/sex-matched patients with IBS bowel symptoms	No increase
Bhansali et al, 2004	India	60/160	65	0	0	Age/sex-matched patients with IBS bowel symptoms	No increase
Terzola et al, 2005[6]	Italy	235/233	49	55 (23)	34 (15)	In-house non-acromegalic symptomatic patients	Increased
Matano et al, 2005	Japan	19/76		8 (42)	13 (17)	In-house non-acromegalic patients	Increased
Matjya et al, 2006	Poland	51/–	53	21 (41)	–	Compared against same sample using autofluorescence colonoscopy	'High prevalence'

Renehan AG et al.; *Best Pract & Res Clin Endocrinol & Metab* 2008

acromegaly & CRC

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- small patient numbers, unadjusted for major confounding factors (eg, age and gender)
- endoscopists are not blind (operator bias)
- colonoscopy is technically more difficult in acromegalic patients → more experienced endoscopists may detect more neoplastic lesions.
- hyperplastic &adenomatous polyps described together
- in population-based studies among cohorts of acromegalic patients, invasive CRC rates range from **0.8% to 1.3%**.

Renehan AG et al.; *Best Pract & Res Clin Endocrinol & Metab* 2008

acromegaly & neoplasms

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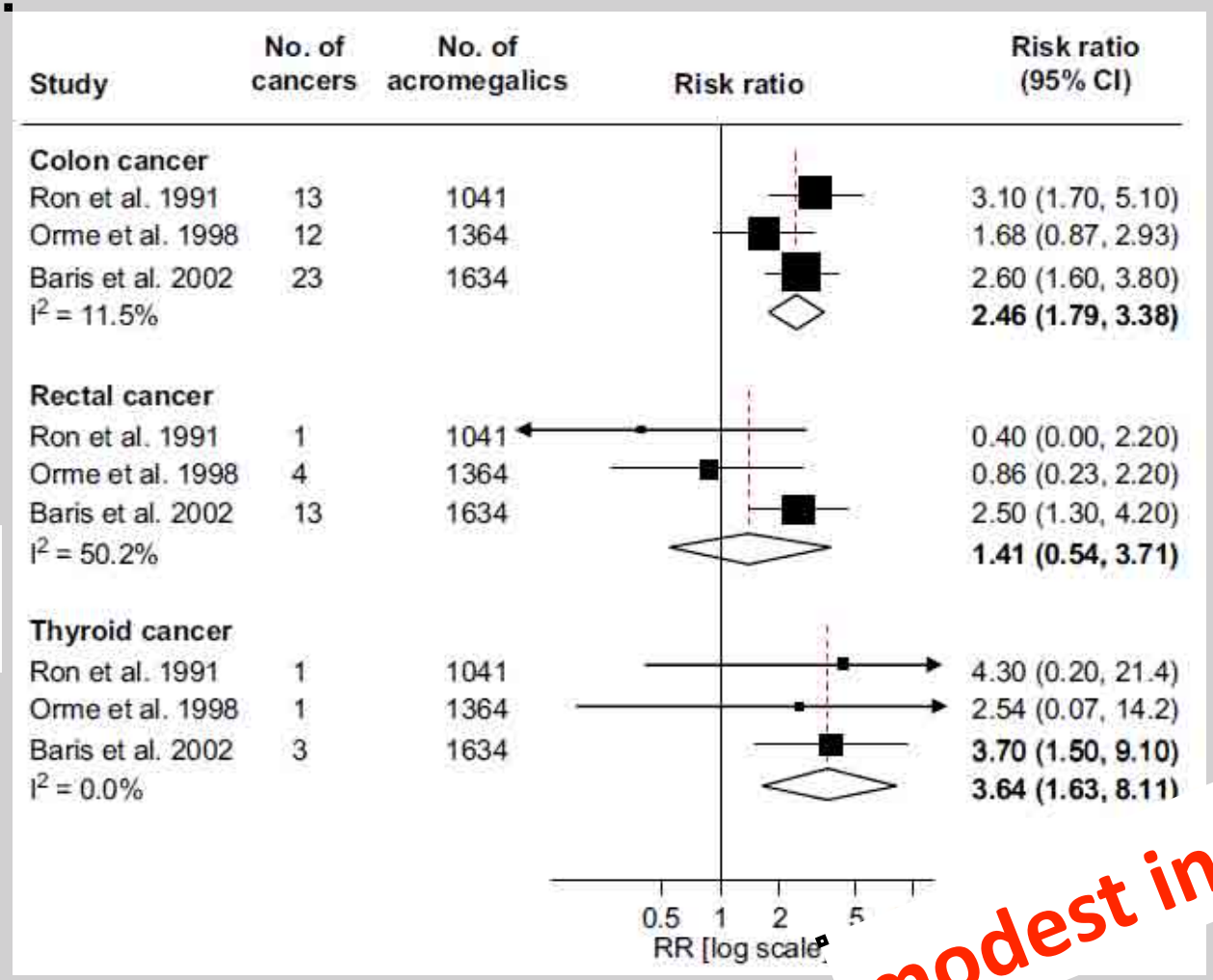
associations of acromegaly with CR and thyroid cancer in population-based studies



modest increase

Renehan ..., *Best Pract & Res Clin Endocrinol & Metab* 2008

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GH therapy

GH/IGF-1 axis & tumors

GH therapy

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1) de-novo cancer in non-cancer patients with GHD

2) tumor recurrence in patients with previously treated cancer and with GHD

3) 2nd neoplasms in survivors of childhood cancer with GHD

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1) de-novo cancer in non-cancer patients with GHD

de-novo cancer in non-cancer patients with GHD

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- Increased fat mass (especially central adiposity)
- Decreased lean body mass
- Decreased muscle strength
- Decreased exercise performance
- Decreased cardiac capacity
- Decreased bone mineral density and increased risk of fracture
- Atherogenic lipid profile
- Thin, dry skin
- Psychosocial problems and decreased quality of life
  - Fatigue
  - Depression
  - Anxiety
  - Impaired sleep
  - Social isolation

GHRT

long-term

- efficacy
- safety
- cost-effectiveness

continuation of therapy generally recommended even after completion of linear growth

de-novo cancer in non-cancer patients with GHD

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increased malignancy risk

- case-reports
- a minority of series
- SAGhE

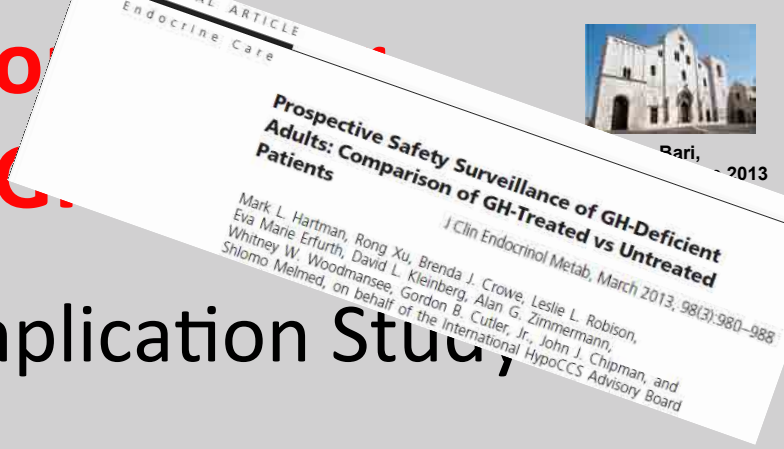
Wada E et al.; *Jpn J Clin Oncol* 1989
Watanabe S et al; *J Pediatr Endocrinol* 1993
Watanabe S et al; *Lancet* 1998
Swerdlow AJ et al.; *Lancet* 2002

not increased malignancy risk

- HypoCCS
- KIMS
- NCGS

Reed ML et al.; *Front Endocrinol* 2013

de-novo cancer in no… patients with C…



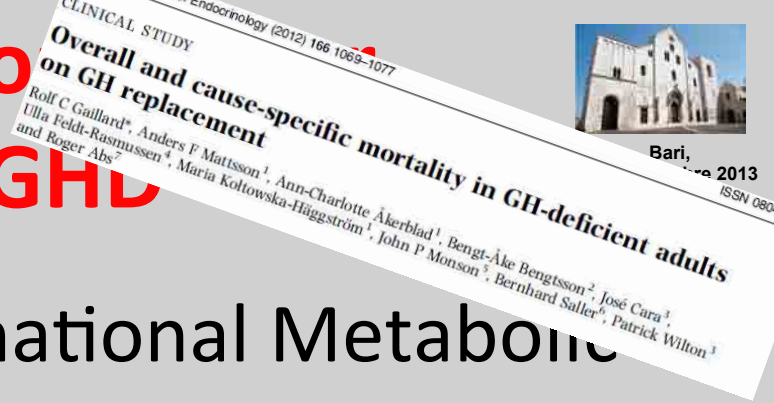
Hypopituitary Control and Complication Study **(HypoCSS)**, Lilly™

- IR of events between GH-treated and untreated **2430** GHD adults
- prospective observational study
- 157 US centers (1996-2002)
- mean follow-up **2.3** years
- no significant difference
  - death
  - new cancer
  - intracranial tumor growth/recurrence
  - DM
  - CV events

	GH-Treated (n = 1988)	Untreated (n = 442)
Cancer type, n (%)		
Skin cancer[b]	10 (0.50)	5 (1.13)
Prostate cancer	3 (0.15)	3 (0.68)
Breast cancer	4 (0.20)	1 (0.23)
Lung cancer[c]	4 (0.20)	0
Colorectal cancer	2 (0.10)	1 (0.23)
Acute leukemia	2 (0.10)	0
Carcinoid tumor	0	1 (0.23)
Lymphoma	0	1 (0.23)
Ovarian cancer	1 (0.05)	0
Ewing's sarcoma	1 (0.05)	0
Pancreatic islet cell tumor	1 (0.05)	0
Bladder/urethral cancer	1 (0.05)	0
Fibrosarcoma	1 (0.05)	0
Laryngeal cancer	1 (0.05)	0
Polycythemia vera	1 (0.05)	0
Total cancers, n (%)	32 (1.61)	12 (2.71)

[a] For total cancer events, there was no significant difference between the 2 groups after controlling for baseline differences ($P = .57$).

de-novo cancer in no[illegible] patients with GHD

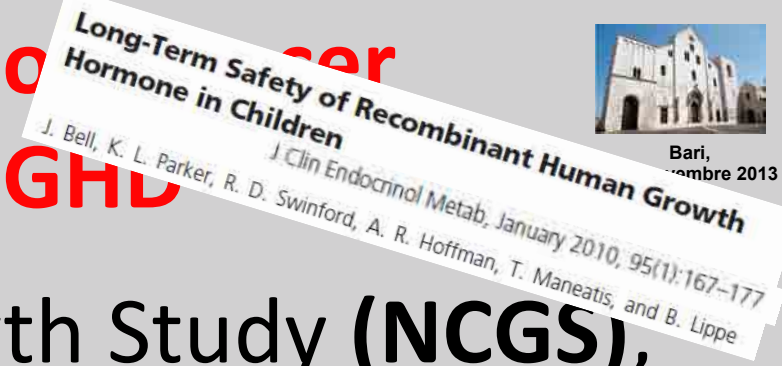


Pfizer™ [formerly Kabi ™] International Metabolic Database **(KIMS)**

- multicentre, non-interventional study
- mortality & associated factors within GHRT adults
- **13,983** GHD patients; 528 deaths
- mean follow-up **4.9** years
- mortality: slightly higher vs. general pop.
- no increased SMR for deaths from CVDs or malignancies

Gaillard RC et al.; *Eur J Endocrinol* 2012

de-novo cancer in no[illegible]cer patients with GHD



Bari, [illegible]embre 2013

National Cooperative Growth Study **(NCGS)**, Genentech™

- multicenter post-marketing surveillance study to monitor safety & efficacy of rhGH
- **54,996** children (1985-2006), 900 investigators
- 20 years of GH therapy
- de-novo malignancies: not significantly increased *vs.* general population
  - leukemia
  - intra/extracranial

TABLE 4. New-onset malignancies without risk factors

Age (yr)	Years of GH exposure	Expected rate per 100,000 yr of exposure	Observed cases	Expected cases
0–4	11,348	20.4	1	2.32
5–9	44,585	11.4	6	5.08
10–14	85,909	12.9	12	11.08
15–19	36,082	20.0	9	7.22
20–24	540	34.9	1	0.19
Total	178,464	14.5[a]	29	25.88

Bell J et al.; *J Clin Endocrinol Metab* 2010

de-novo cancer in [illegible] patients with GH


Long-Term Mortality after Recombinant Growth Hormone Treatment for Isolated Growth Hormone Deficiency or Childhood Short Stature: Preliminary Report of the French SAGhE Study
Jean-Claude Carel, Emmanuel Ecosse, Fabienne Landier, Grégoire Rey, and Joël Coste
Djamila Meguellati-Hakkas, Florentia Kaguelidou,
J Clin Endocrinol Metab, February 2012, 97(2):416–425

Bari, [illegible]embre 2013

Safety and appropriateness of Gh treatment in Europe **(SAGhE)**

- population-based study on long-term safety of rhGH in French children
- 6928 children (1985-1996) with low-risk
- mean follow-up: 17.3 years
- all-cause mortality increased (SMR 1.33) vs. general pop.
  - all-type cancer mortality non increased (CRC, Hodgkin…)
  - bone tumor-related mortality increased (SMR 5.00)
- GH doses >50mcg/kg/day associated with mortality rates

de-novo cancer in non-cancer patients with GHD

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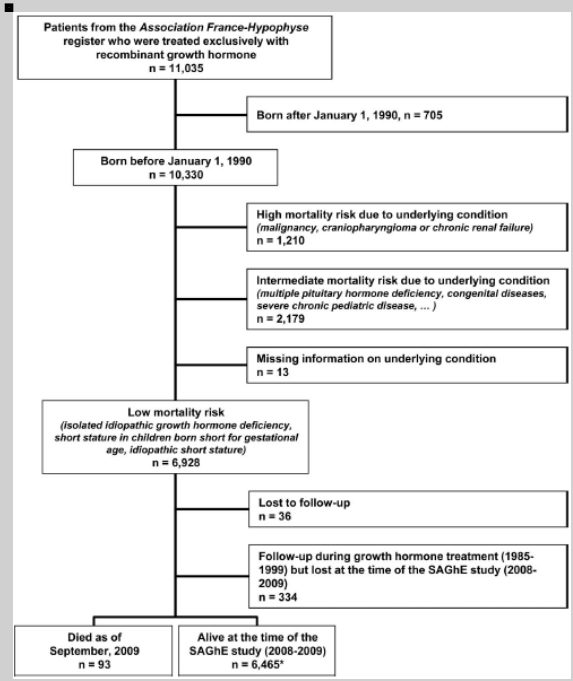
Safety and appropriateness of Gh treatment in Europe **(SAGhE)**

Long-Term Mortality after Recombinant Growth Hormone Treatment for Isolated Growth Hormone Deficiency or Childhood Short Stature: Preliminary Report of the French SAGhE Study

J Clin Endocrinol Metab, February 2012, 97(2):416–425

Jean-Claude Carel, Emmanuel Ecosse, Fabienne Landier,
Djamila Meguellati-Hakkas, Florentia Kaguelidou, Grégoire Rey, and Joël Coste



Duration of follow-up				
Duration of follow-up after the end of treatment (yr)				
≤5 (n = 6402)	31	25.93	1.20	(0.81–1.70)
≤10 (n = 6402)	57	46.32	1.23	(0.93–1.59)
≤15 (n = 6402)	83	61.38	1.35	(1.08–1.68)
Time after the end of treatment (yr)				
≤5 (n = 6402)	31	25.93	1.20	(0.81–1.70)
>5 and ≤10 (n = 6035)	26	20.39	1.28	(0.83–1.87)
>10 and ≤15 (n = 5316)	26	15.06	1.73	(1.13–2.53)
			P_{trend} 0.17	

Neoplasms (140–239)	7	6.89	1.02	(0.41–2.09)
Malignant neoplasm of lymphatic and hematopoietic tissue (200–208)	2	1.36	1.47	(0.17–5.31)
Malignant neoplasm of bone and articular cartilage (170)	3	0.60	5.00	(1.01–14.61)
All other neoplasms[b]	2	4.93	0.41	(0.05–1.46)

"Overall, our results do not allow the conclusion of the causal role of GHtreatment in the findings but highlight the need for additional studies on long-term morbidity and mortality after GHtreatment in childhood, in particular when high doses have been used"

1) de-novo cancer in non-cancer patients with GHD

inconclusive evidence of a very modest increase in cancer risk

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2) tumor recurrence in patients with previously treated cancer & with GHD

tumor recurrence in patients with previously treated cancer & with GHD

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7-10 novembre 2013

not increased risk

Arslanian SA et al., *Am J Dis Children* 1985

- Rodens KP et al., *Acta Endocrinol* 1987
- Clayton PE et al., *Lancet* 1987
- Ogilvy-Stuart AL et al., *BMJ* 1992
- Swerdlow AJ et al., *J Clin Endocrinol Metab* 2002

Major studies of growth hormone treatment and risk of tumor recurrences

Study	N	Patient-years on growth hormone treatment	Principal malignancy type(s)	Risk estimate
Ogilvy-Stuart et al [105]	53	–	brain tumors	RR 0.8
Sklar et al [98]	172	–	brain tumors	RR 0.8
Swerdlow et al [104]	180	–	brain tumors	RR 0.6
Blethen et al [96]	19,000	47,000	leukemia	no increased risk
Maneatis et al [97]	33,161	113,000	leukemia	SMR 0.7
			nonleukemic neoplasms	SMR 0.4
Wyatt [95]	~33,000	135,431	nonleukemic neoplasms	SIR 0–1.6

- **NCGS**
  - not increased risk of leukemia/brain tumors recurrences
- **CCSS**
  - 13,539 survivors of pediatric tumors
  - 361 GH treated pts; follow-up: 6.2 years
  - RR of disease recurrence: not increased (0.83; 95% CI 0.37-1.86; $P = 0.65$)
  - RR of mortality: not increased (1.21; 95% CI 0.75-1.94; $P = 0.43$)

tumor recurrence in patients with previously treated cancer & with GHD

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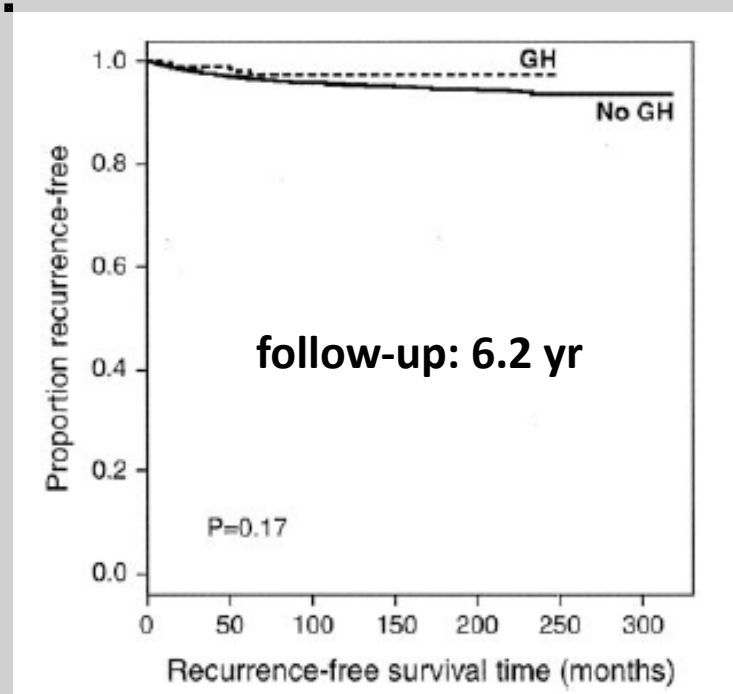
Childhood Cancer Survivor Study (CCSS)

retrospective cohort of 5-yr survivors of childhood cancer diagnosed <21 yr, between 1970 and 1986, and treated in USA/Canada

- currently, overall 5- yr survival rate for childhood cancer: >70%
- most prevalent late effects of cancer therapy: endocrine disorders (40%)
- GHD: up to 30-40%



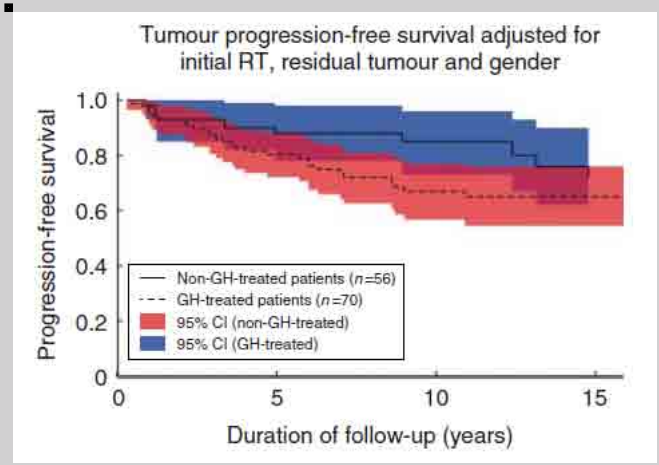
Sklar CA et al.; *J Clin Endocrinol Metab* 2002

tumor recurrence in patients with previously treated cancer & with GHD

Bari,
7-10 novembre 2013

Craniopharyngioma

- case-control study
  - GHD caused by craniopharyngioma
  - rhGH > 3 years *vs.* no therapy
- 56 patients
- mean duration of GHRT: 13.6 years



long-term GHRT did not affect the PFS

Olsson DS et al.; *Eur J Endocrinol* 2012

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2) tumor recurrence in patients with previously treated cancer & with GHD

the general evidence suggests no increased risk

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7-10 novembre 2013

3) 2nd neoplasms in survivors of childhood cancer with GHD

2nd neoplasms in survivors of childhood cancer with GHD

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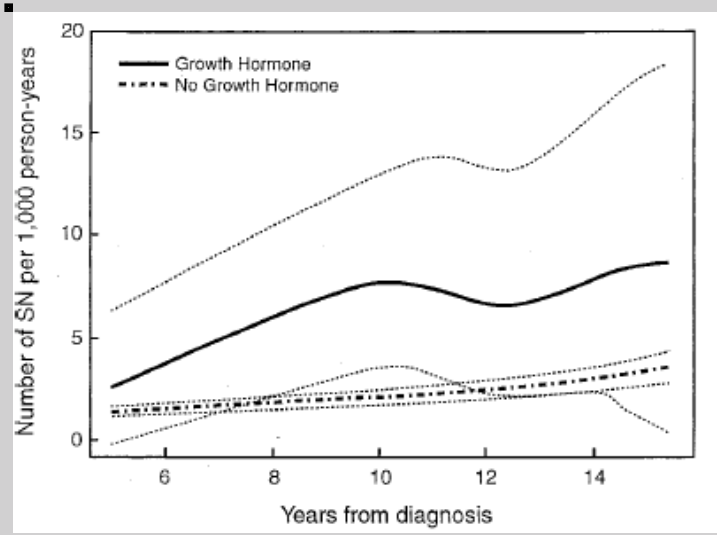
Childhood Cancer Survivor Study (CCSS)

- 13,539 survivors of pediatric tumors
- 361 GH treated pts; follow-up: 6.2 years
- RR of 2nd neoplasms **3.21** (95% CI 1.88-5.46; *P* < 0.0001)
- excess of solid tumors in GH-treated survivors of acute leukemia

Diagnosis	RR (95% CI)	*P*
Acute leukemia	4.98 (1.95–12.74)	<0.001
CNS tumors	2.34 (0.96–5.70)	0.06
CNS tumors (meningiomas excluded)	1.46 (0.31–6.79)	0.69
Rhabdomyosarcoma	1.82 (0.41–8.01)	0.43



Sklar CA et al.; *J Clin Endocrinol Metab* 2002

2nd neoplasms in survivors of childhood cancer with GHD

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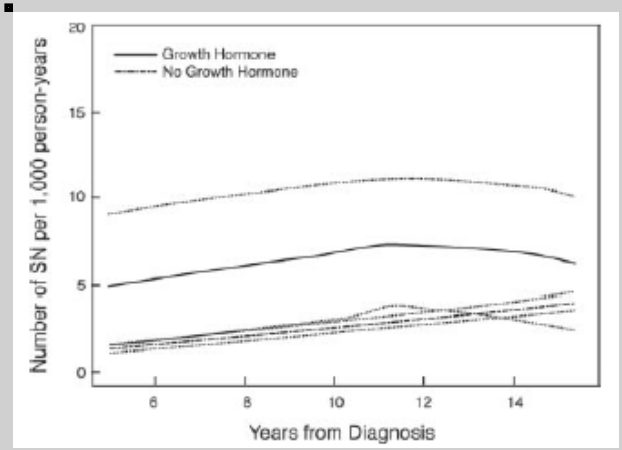
7-10 novembre 2013

Childhood Cancer Survivor Study (CCSS)

- 14,108 survivors of pediatric tumors
- 361 GH treated pts; follow-up: 8.8 years
- RR of 2nd neoplasms **2.15** (95% CI 1.3-3.5; *P* < 0.002)
- excess of solid tumors in GH-treated survivors of acute leukemia
- meningiomas: the most common 2nd tumor
- *the elevation of risk due to GH use diminish increasing follow-up*



Ergun-Longmire E et al.; *J Clin Endocrinol Metab* 2006

2nd neoplasms in survivors of childhood cancer with GHD

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- **NCGS**: increased risk with rhGH in pts with a prior history of malignancy, exp. leukemia and previously irradiated pts
- GH could induce mitogenic activity in cells already predisposed to neoplastic change and hence increase the theoretical risk of developing 2nd neoplasms
- The increased risk of developing 2nd neoplasms in GH-treated childhood cancer survivors is now listed in U.S. labeling for all rhGH products

Bell J et al.; *J Clin Endocrinol Metab* 2010

2nd neoplasms in survivors of childhood cancer with GHD

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Genetics and Neuroendocrinology of Short Stature International Study **(GeNeSIS)** + Hypopituitary Control and Complication Study **(HypoCSS)**, Lilly™

- retrospective analysis of 2 prospective cohort studies
  - childhood cancer survivors (GeNeSIS)
  - GHD adults (HypoCSS)
- incidence of 2nd tumors: consistent with increased risk
- estimated cumulative incidence of 2nd tumors after 5 yr of follow-up:
  - 6.2% GeNeSIS
  - 4.8% HypoCSS
- most common: meningiomas (nearly all, after CT/RT exposure)

Woodmansee WW et al.; *Eur J Endocrinol* 2013

2nd neoplasms in survivors of childhood cancer with GHD

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7-10 novembre 2013

retrospective study of 50 CCSs who developed GHD due to cancer therapies from a specialized outpatient clinic

Transition Unit for Childhood Cancer Survivors – Città della Salute e della Scienza Hospital of Turin

- cumulative incidence of 2nd neoplasms between pts treated with rhGH during childhood and pts who did not: **no difference**
- follow-up: 20 years
- high incidence of 2nd neoplasms: **28%!**
- most common 2nd neoplasms: menigioma, basal cell ca.
- elapsed time to the 2nd neoplasm: shorter in GHD-treated pts (17.0 *vs.* 24.7 yrs)

- all 2nd neoplasms **in pts treated with RT!**

Brignardello E et al. (in press)

2nd neoplasms in survivors of childhood cancer with GHD

Bari,
7-10 novembre 2013

GH and IGF-1 have a promoting rather than initiating effect on carcinogenesis → GH could accelerate the growth of 2nd neoplasms

Key messages:

- GHRT worthy to CCSs during childhood, to obtain normal height w/o increased risk of cancer
- however, 2nd neoplasms seem to arise earlier: close follow-up!
- in adult survivors, the indication for GHRT are less obvious

Brignardello E et al. (in press)

3) 2nd neoplasms in survivors of childhood cancer with GHD

some evidence of a modest increased risk associated with GH usage

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7-10 novembre 2013

Terapie endocrino-metaboliche e rischio oncologico

Grazie!

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