Thyroid cancers after the Chernobyl accident; lessons learnt, an update.

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- *What is the size of the increase in thyroid carcinomas and does it continue?*
- *What are the uncertainties in assessing the size of the increase?*
- What is the estimated risk/Gy
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- The future

- The WHO/IAEA conference considering the first 20 years after the Chernobyl accident found that about 4000 cases of thyroid cancer could be attributed to the accident.
- It was not made clear in the press release that this applied only to the most exposed areas.

Thyroid Ca in Belarus in those exposed to the accident, 1986-mid2006

Oblast	Children	Adolescents	Adults	Total
Brest	166	128	1523	1817
Gomel	382	234	2377	2993
Grodno	48	21	638	707
Minsk	45	33	1417	1495
Minsk City	67	41	2383	2491
Mogilev	45	31	1783	1859
Vitebsk	13	19	1601	1633
Belarus	766	507	11,722	12,995

From Bespalchuk et al, Nagasaki Symposium,2007

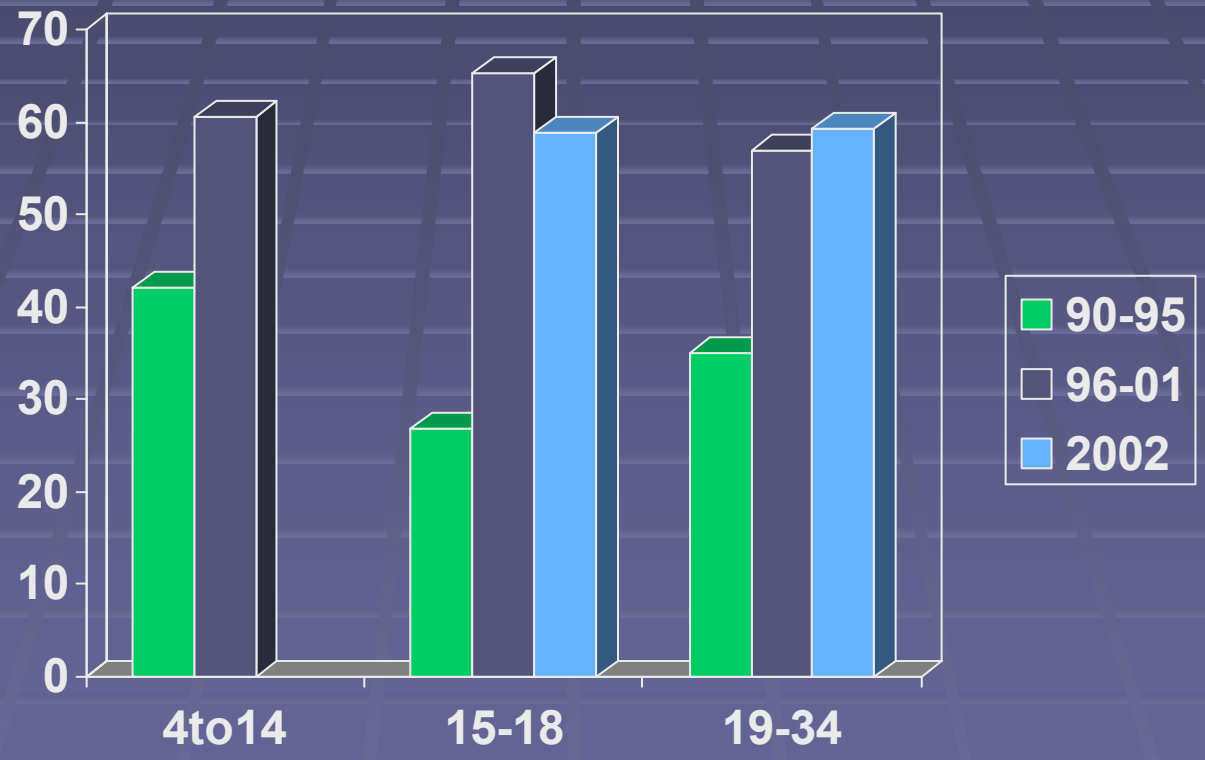
Predictions for numbers of cases of thyroid cancer due to radiation occurring in Europe from 1986 to 2056

- 15,700. 14,100 of these due to exposure before age of 15. Cardis et al, 2006, Int J Cancer, 119: 1224-1235
- 92,627. 26,584 of these predicted to lead to death. Malko, quoted by Yablokov and Nesterenko, 2009, Ann NY Acad Sci, 1181: 1-220

Uncertainties in assessing size of increase

- Increased ascertainment through screening, increased awareness, diagnostic advances
- Area covered
- Problems of diagnosis in peripheral hospitals
- Increasing PTC incidence in non-exposed areas
- Separation of radiogenic from background (baseline) incidence

Thyroid PTCs from Ukraine born after 1967.
% of tumours 2cm or less by age at operation



Data from Tronko et al 2005, BMU 2005-668

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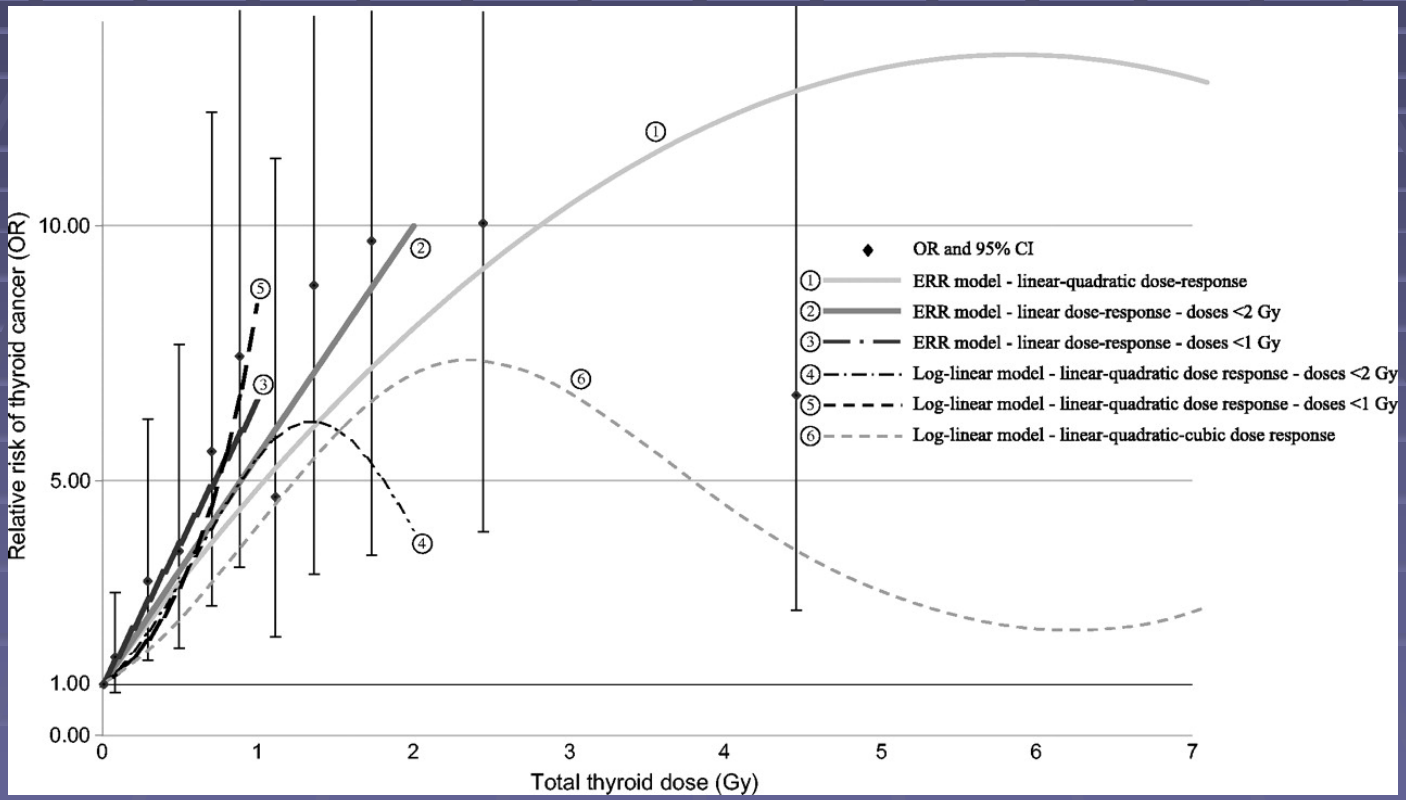
Estimation of risk/Gy and factors influencing risk

- Dose, (RR 5.5-8.4/Gy (Cardis 2005))*
- Age at exposure
- Gender
- Environment
- Genetic susceptibility
- Time of assessment

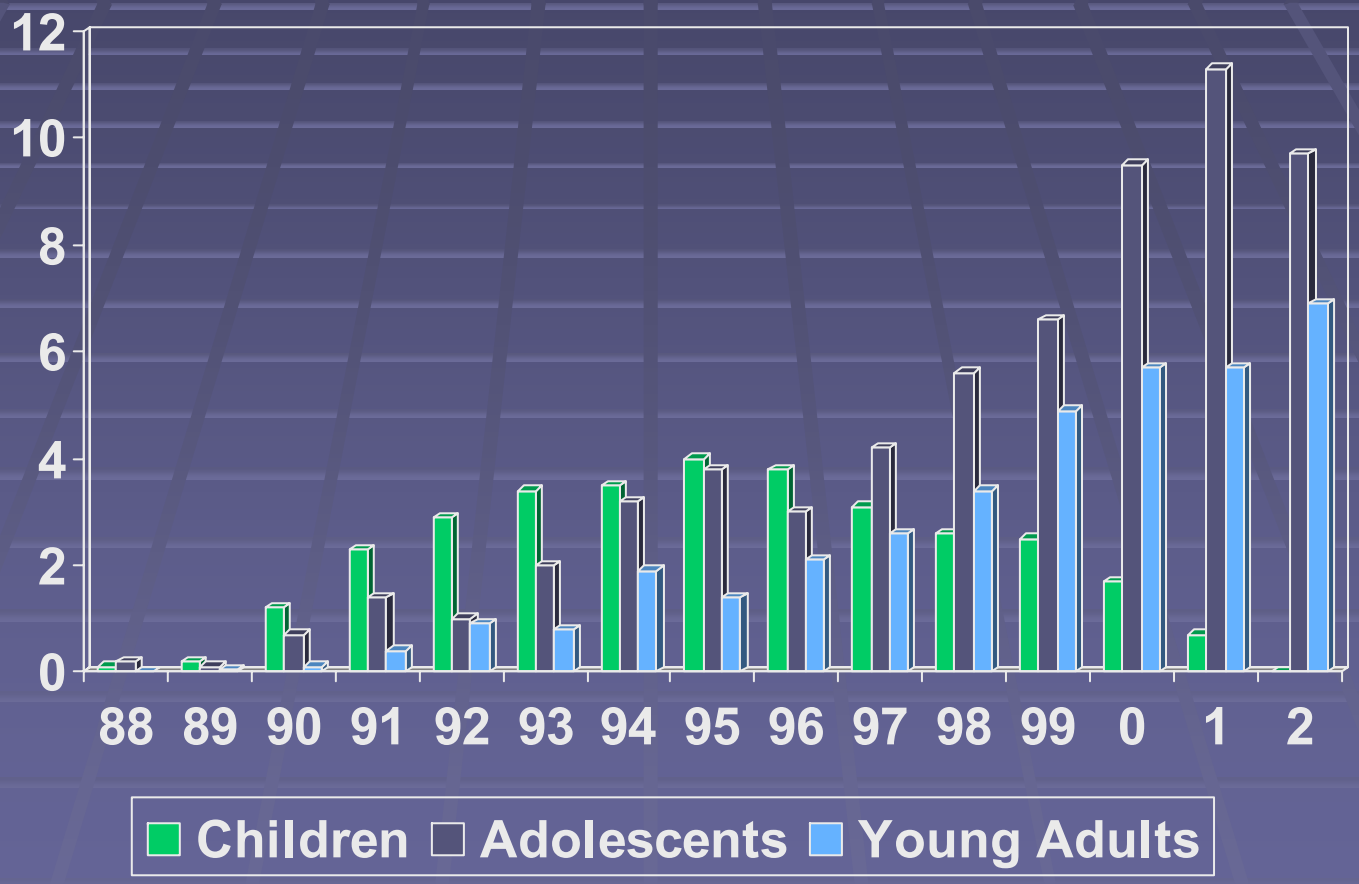
*Very recent publication estimates ERR as 2.15/Gy (95%CI 0.81-5.47). Zablotska et al,BJCancer 23.11.10

Comparison of odds ratios (ORs) predicted by the best-fitting risk models with categorical odds ratios estimated in 11 dose categories

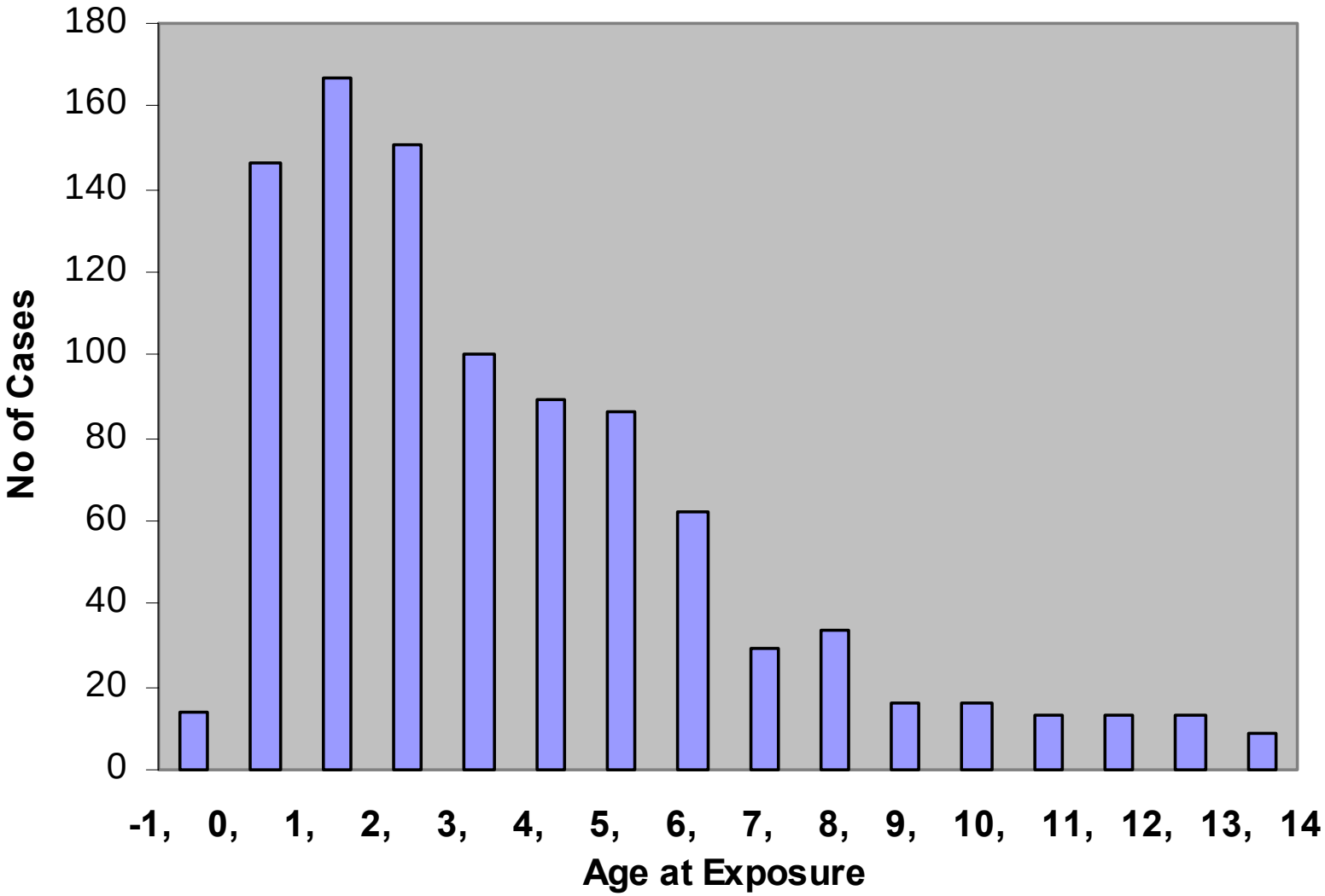


Cardis, E. et al. J. Natl. Cancer Inst. 2005 97:724-732; doi:10.1093/jnci/dji129

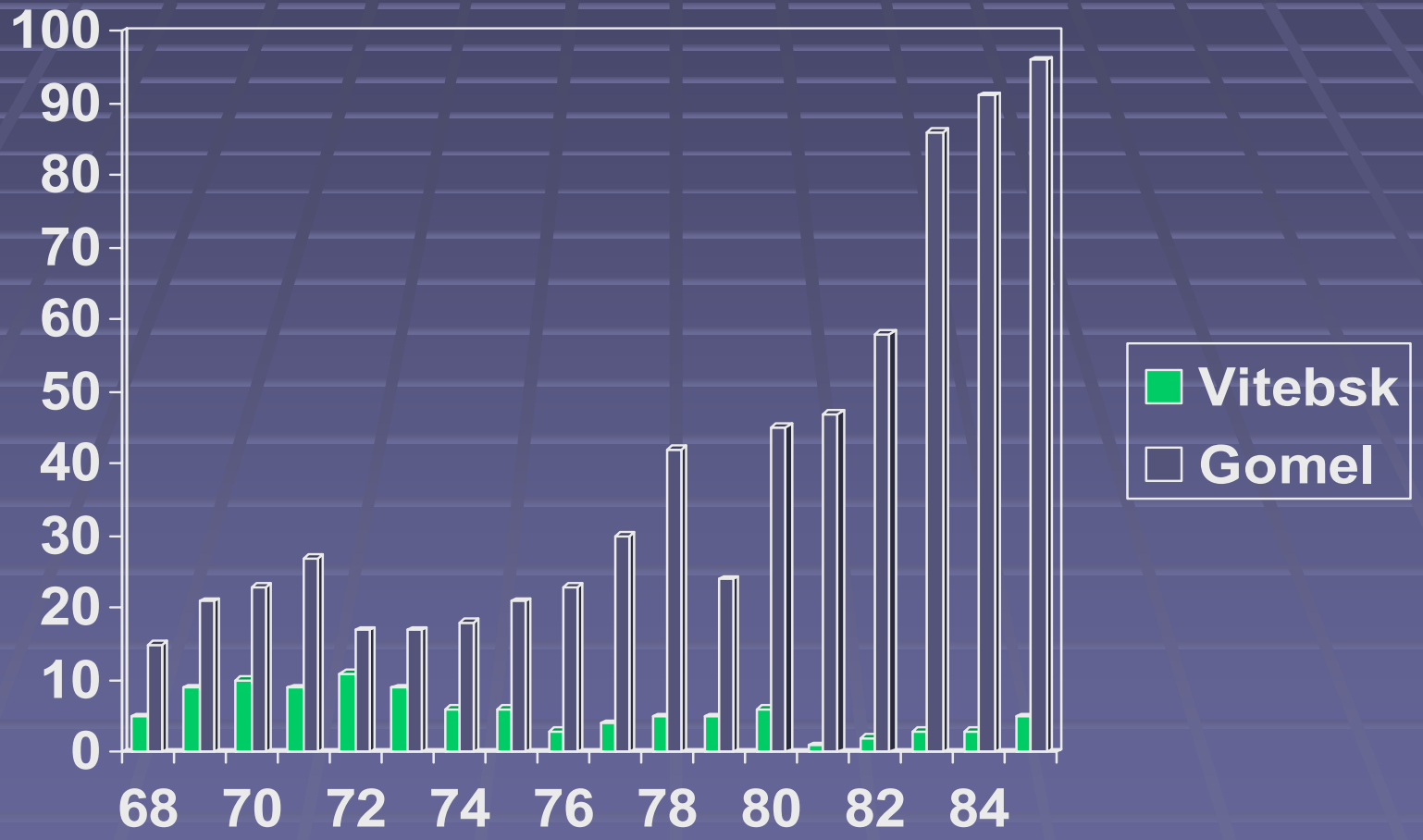
Incidence of thyroid cancer in Belarus. Rate per 100,000



Data from Cardis et al 2006

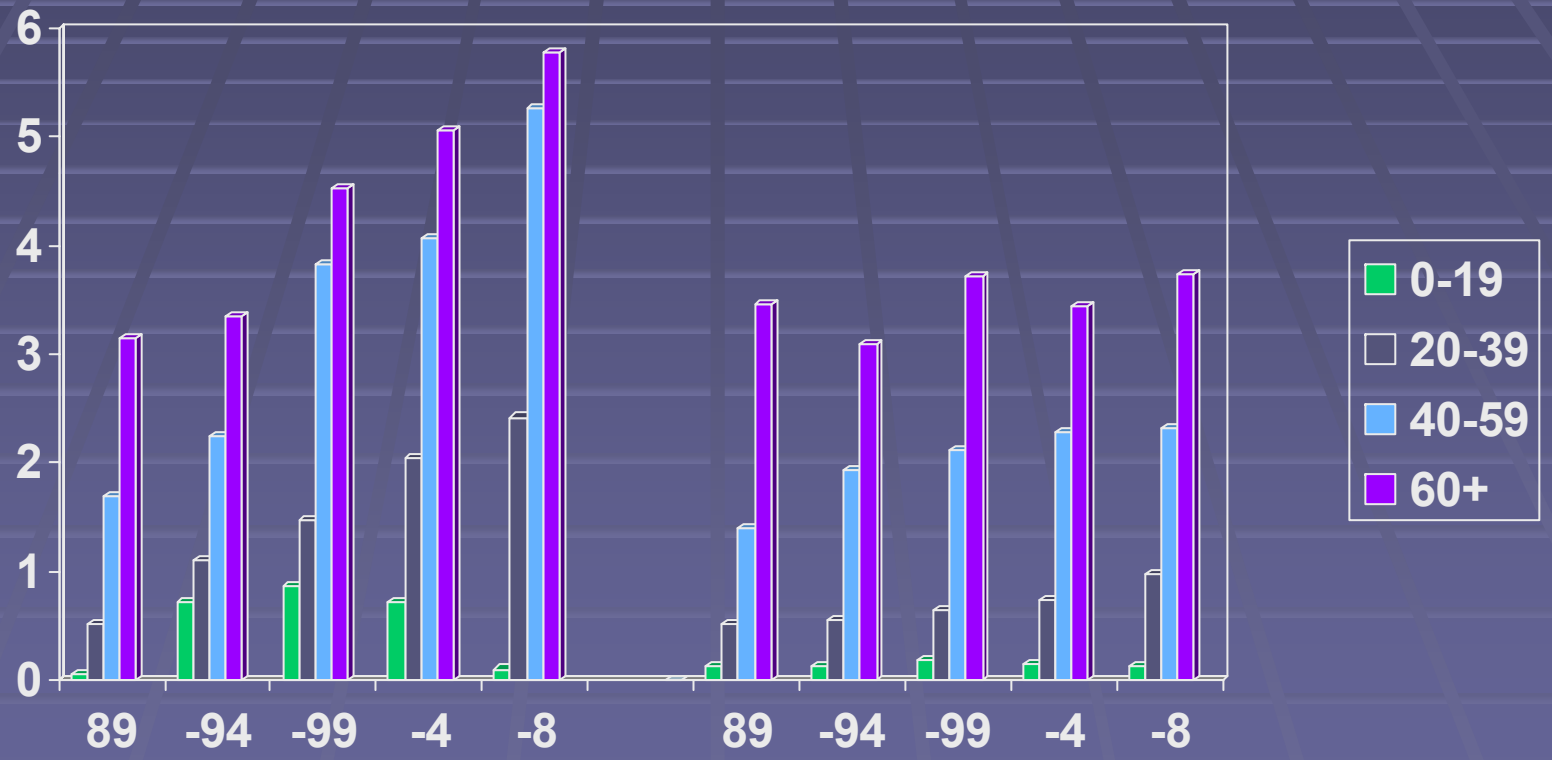

Childhood Thyroid Cancer, Belarus 1990-97
No of Cases
180
160
140
120
100
80
60
40
20
0
-1, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
Age at Exposure

Numbers of Thyroid Ca. in the highest and least exposed oblasts of Belarus by year of birth (<19 at op)



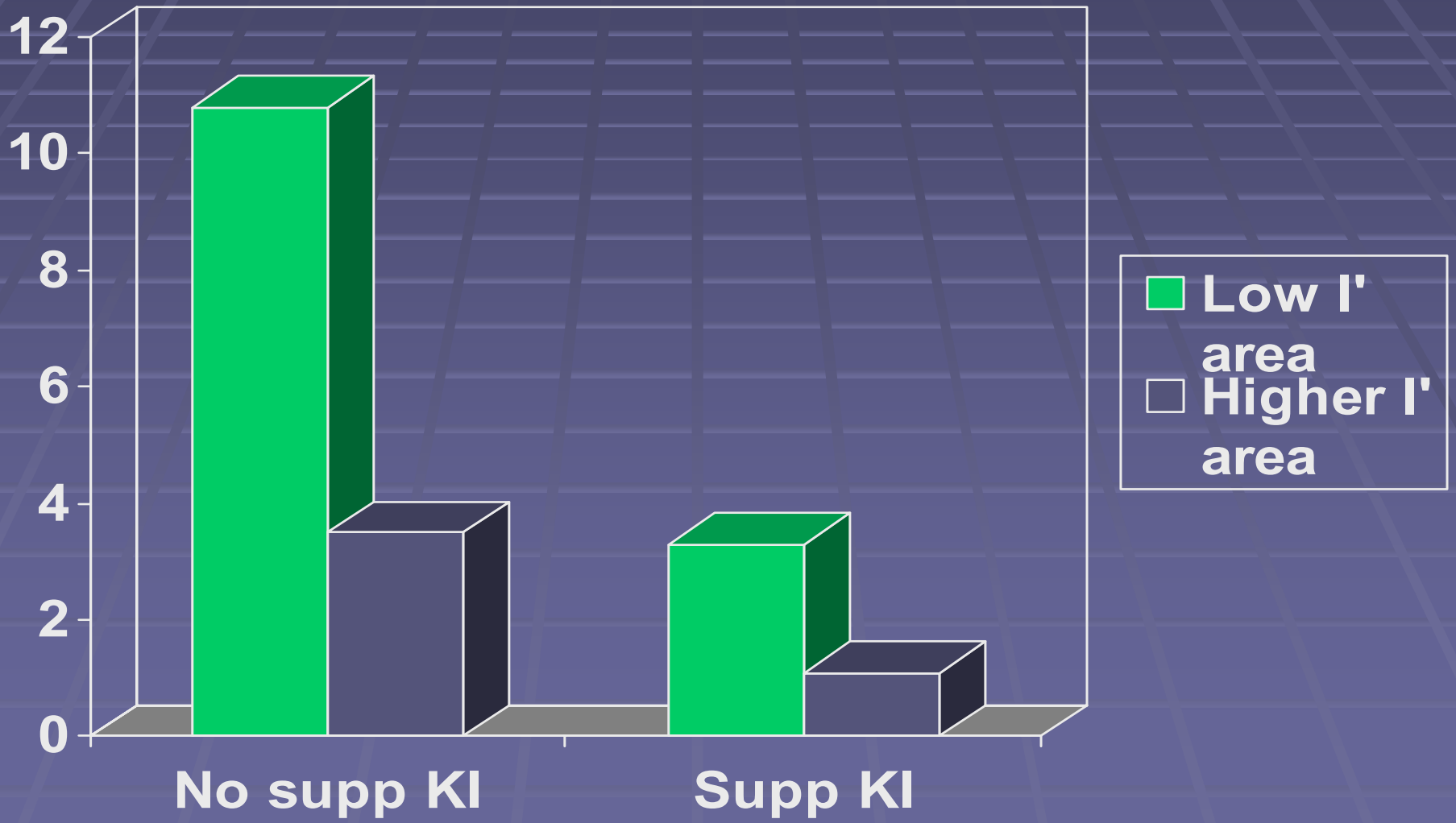
Data from Yu Demidchik 2005 BMU 2005-668

Thyroid Ca incidence rates for males in high and low exposure regions of Ukraine



Data from Fuzik et al, 2010, Rad Env Biophys; online 10.11.10

Thyroid cancer risk and I’ intake
Odds ratio, 1 Gy vs no exposure



From Cardis et al JNCI 2005

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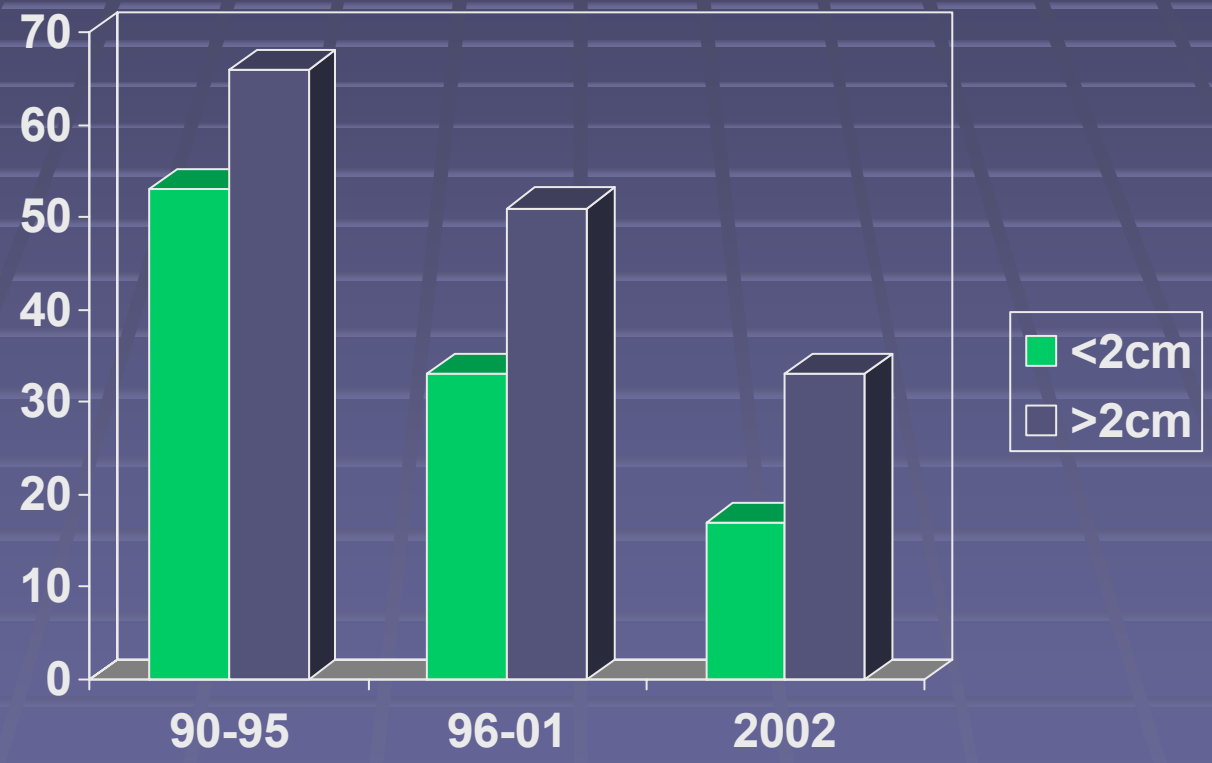
Changes with latency

- Clinical. Tumours are becoming less aggressive
- Pathology. More differentiated and smaller PTCs, less extrathyroid invasion, probable increase in follicular adenomas
- Molecular biology. Overall reduction in PTC rearrangements, fewer RET-PTC3 and more RET-PTC1

Extra-thyroid invasion (%) in PTCs, aged under 19 at exposure



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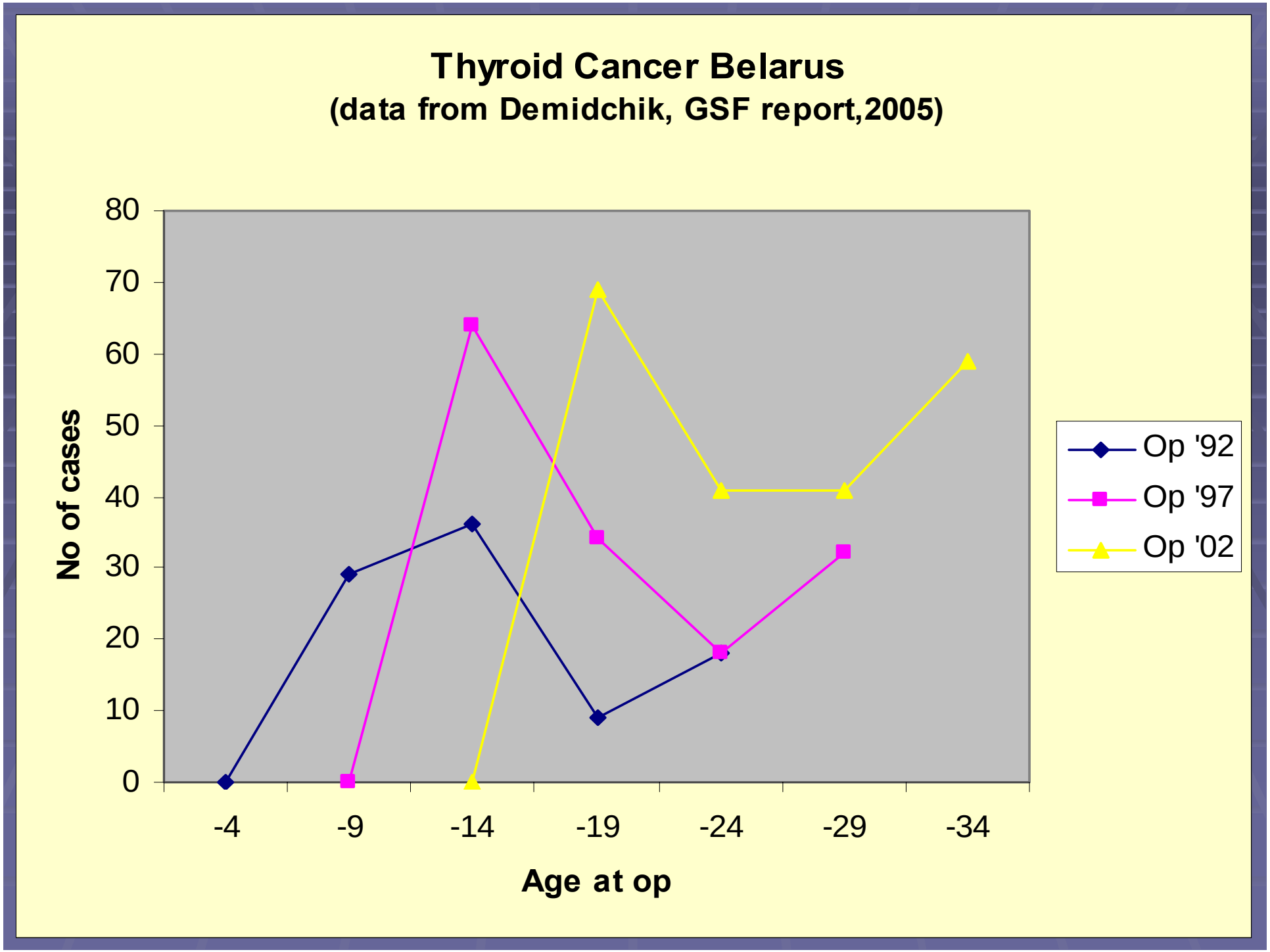
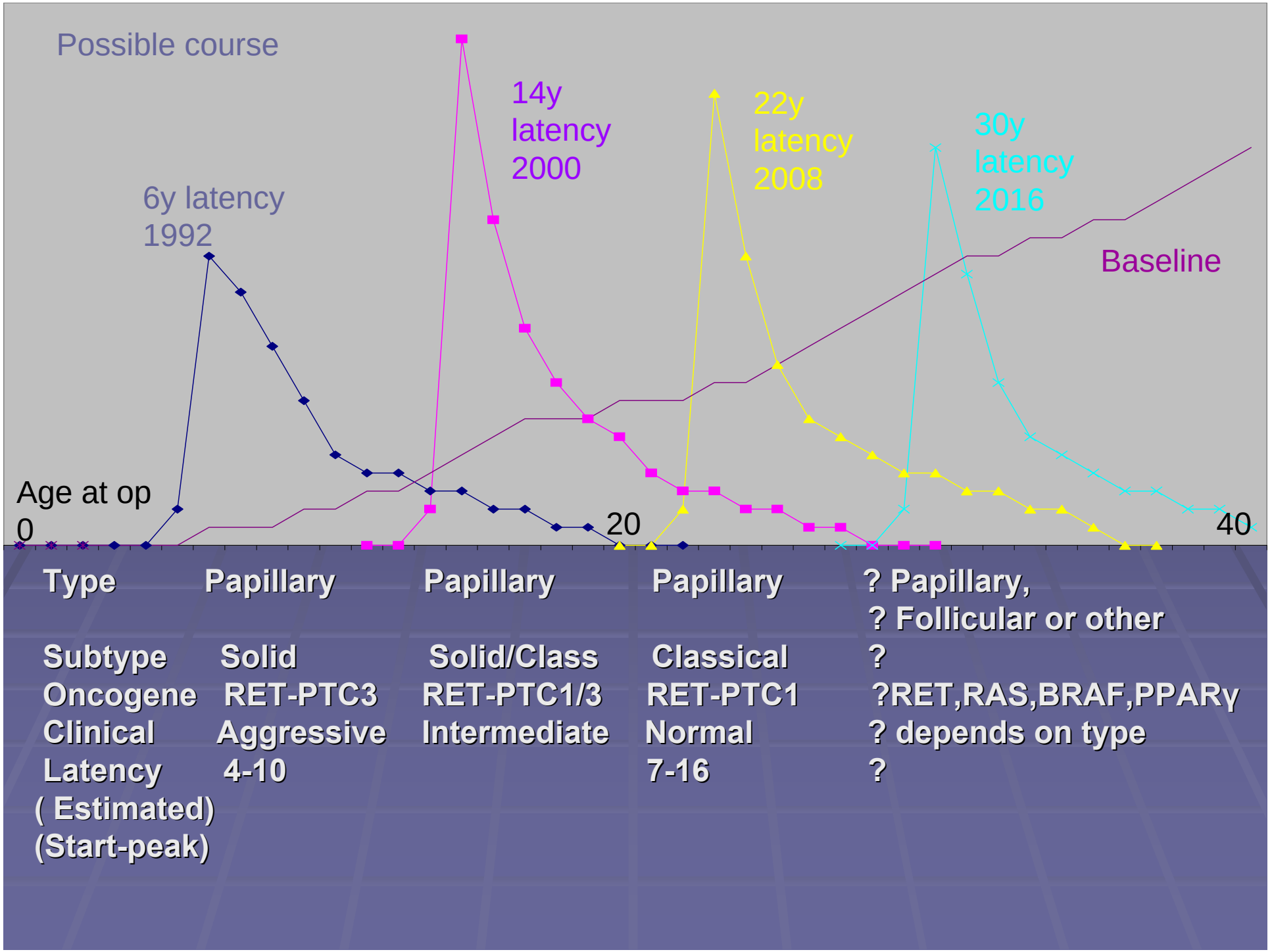

Thyroid Cancer Belarus
(data from Demidchik, GSF report,2005)
No of cases
80
70
60
50
40
30
20
10
0
-4
-9
-14
-19
-24
-29
-34
Age at op
Op '92
Op '97
Op '02



Type	**Papillary**	**Papillary**	**Papillary**	**? Papillary, ? Follicular or other**
Subtype	**Solid**	**Solid/Class**	**Classical**	**?**
Oncogene	**RET-PTC3**	**RET-PTC1/3**	**RET-PTC1**	**?RET,RAS,BRAF,PPARγ**
Clinical	**Aggressive**	**Intermediate**	**Normal**	**? depends on type**
Latency (Estimated) (Start-peak)	**4-10**		**7-16**	**?**

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Do the molecular findings provide a radiation marker?

- The great majority of PTCs from non-exposed areas show either a BRAF or a RET-PTC mutation, in children BRAF is less common.
- Chernobyl PTCs show fewer BRAF mutations than expected

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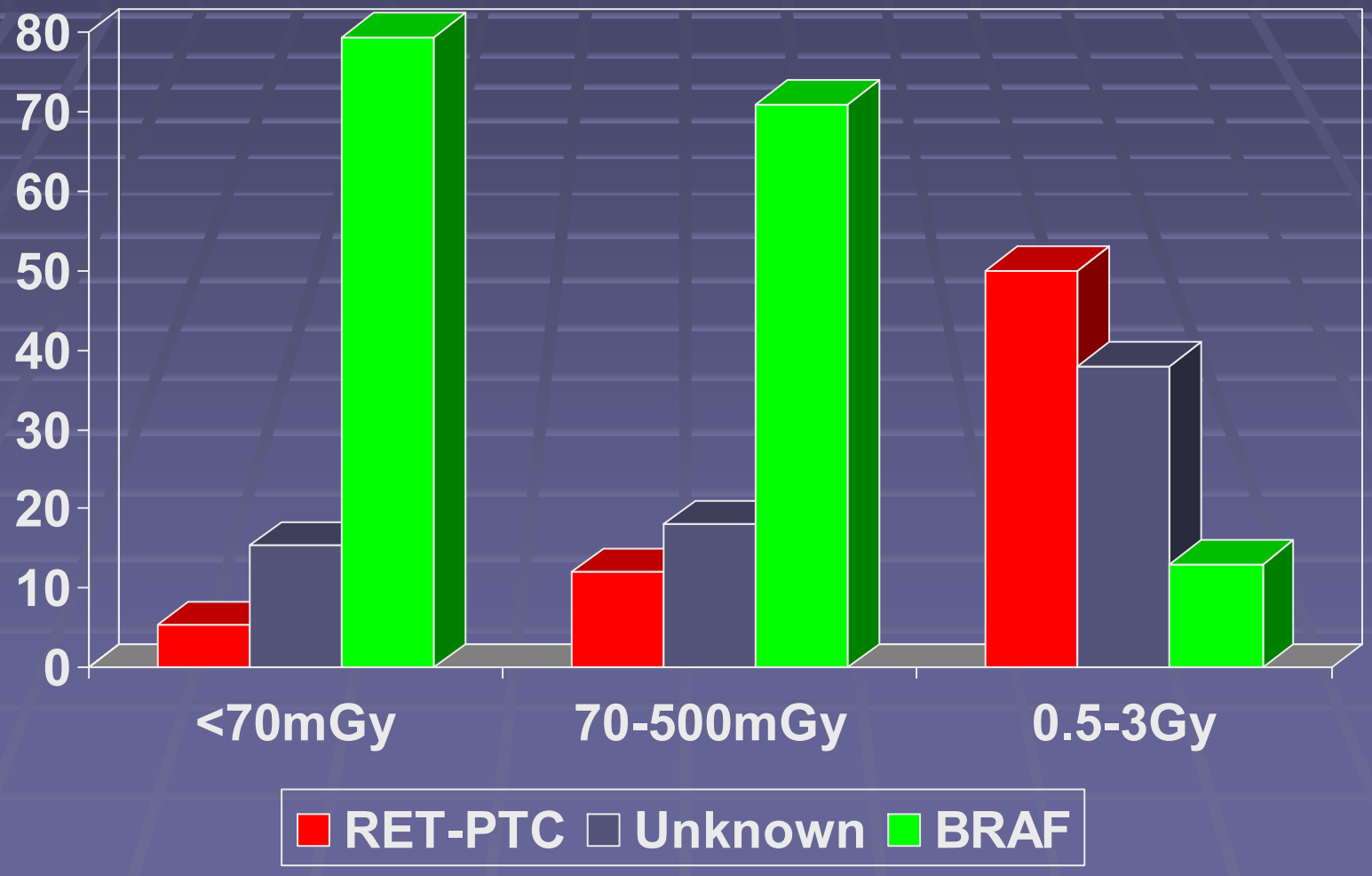
Major oncogene mutations identified in Papillary Thyroid Carcinomas

- RET. Activated by rearrangement to give a RET-PTC oncogene (c15 variants). RET-PTC 1 and 3 by far the most common
- B-RAF. Activated by point mutation, very nearly always V600E. Very rarely activated by rearrangement
- Others. Uncommon. TRAK rearrangements, RAS point mutations, unknown

Papillary Thyroid Carcinoma, genes and radiation dose



Data from Hamatani et al, 2008 Cancer Res 68 7176

- These findings suggest that mutations due to double strand breaks are more common than point mutations as the initial event in radiation induced tumours
- This may be the only ‘molecular marker’ of radiation induced neoplasia

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A pragmatic approach to assessing the radiation risk to the thyroid

- The change in risk with age at exposure poses a problem.
- To include all under 14 in one category conceals wide variation.
- The evidence from Chernobyl suggests that those under 3 show much higher risks than older children, it is unclear how much of this is due to greater uptake.
- Studies of external radiation chose 0-4

- On the basis of the current evidence it would seem sensible to subdivide the childhood risk into two groups, categorising young children as high risk, older children as medium risk, young adults as low risk, and older adults as undetectable or no risk.
- This would have the advantage of ensuring that in any future accident measures to protect preschool children would be given priority

- A study should be commissioned to review all the Chernobyl related studies, to reanalyse using differing age groups to justify subdividing children into two groups. Risk/Gy is not the appropriate basis for determining this.

  A study of the risk to adults is also urgently needed, because of conflicting data.

  The evidence in relation to dietary iodine strengthens the need to eliminate I deficiency, and to consider long term iodine supplementation after exposure.

Conclusions

- Exposure to fall-out from Chernobyl has led to a very large increase in the incidence of thyroid carcinoma due to I’ radioisotopes.
- The risk is heavily dependent on age at exposure, and on stable iodine intake.
- Tumour morphology and molecular findings correlate and change with latency.
- Those exposed at a young age continue to carry the increased risk with them into adulthood.

Conclusions continued

- The risk continues in those who were young at exposure
- Consideration should be given for regulatory purposes to define the risk for preschool children separately from older children
- Although morbidity from thyroid cancer is high in the heavily exposed young children, mortality from thyroid cancer in those exposed to Chernobyl is currently extremely low

Future studies

- Effects across Europe of low dose exposure
- Continuing study of the thyroid carcinomas to determine possible changes in tumour type and mutations, and length of outbreak
- Non thyroid studies, including inherited effects
- Follow up of children treated with high dose RAI
- Comprehensive and coordinated long term studies of the consequences of Chernobyl are needed: the EC should take the lead in setting up a Chernobyl Health Effects Research Foundation as a virtual equivalent to the RERF