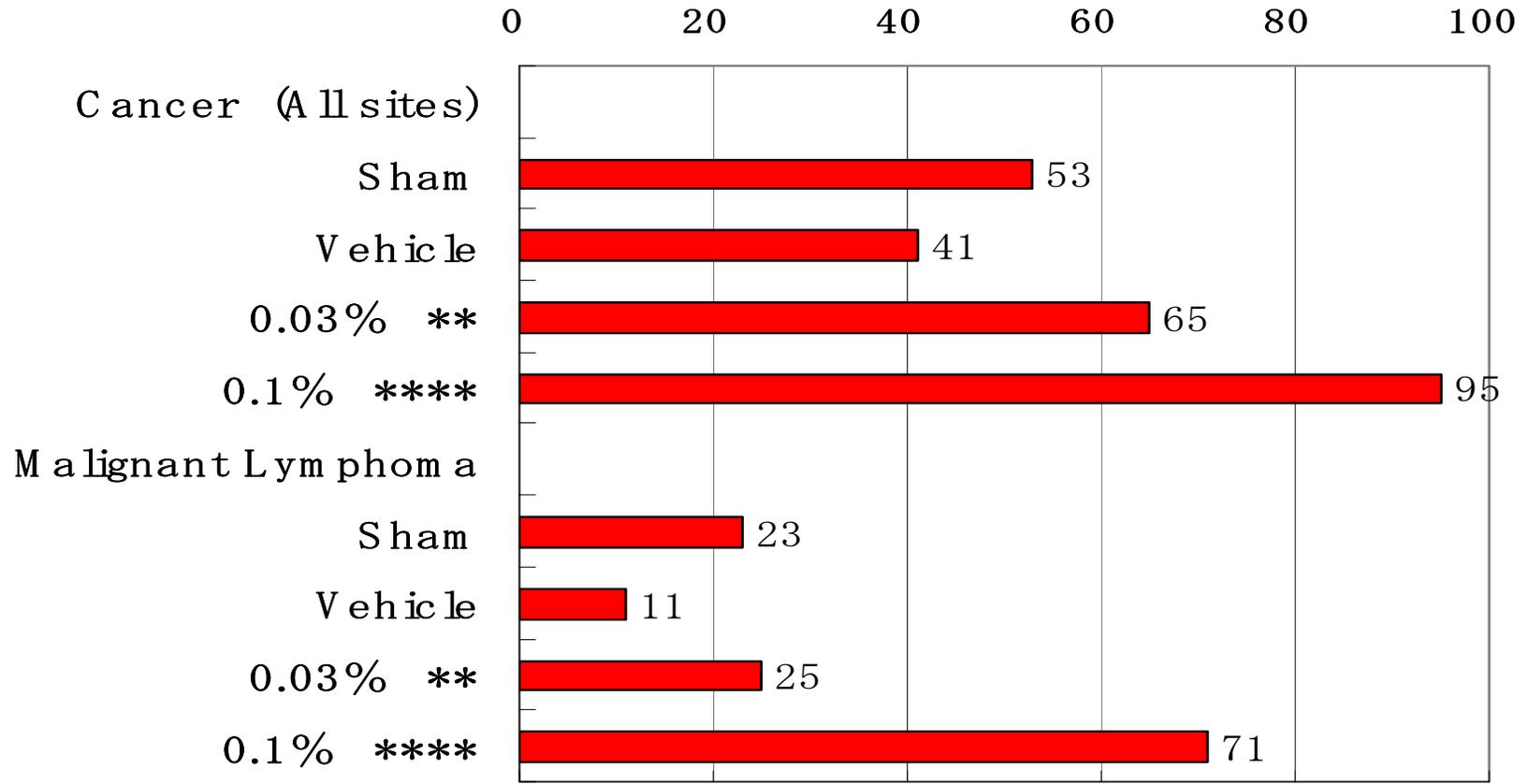


# Tacrolimus

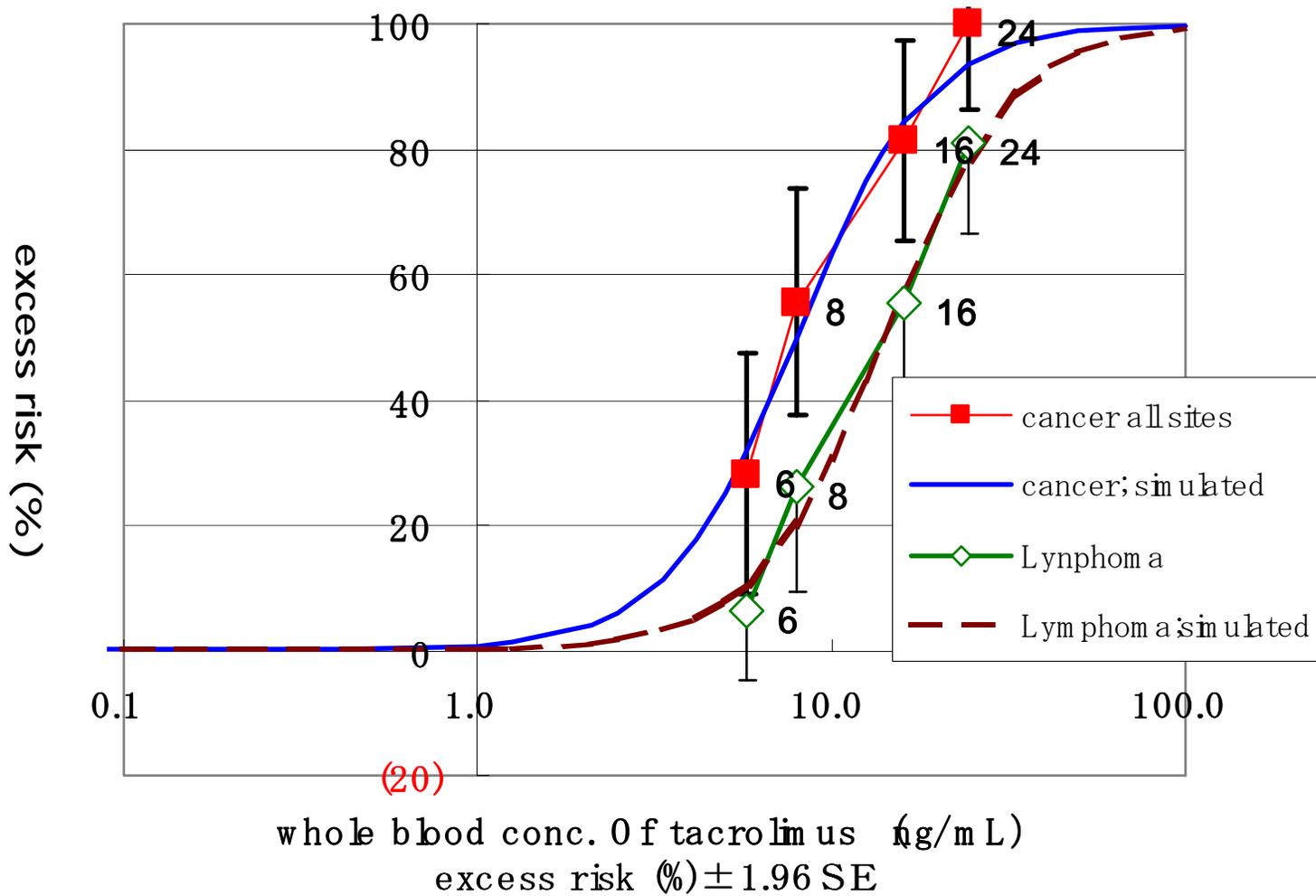
- Tacrolimus (Tac) : Immunosuppressant
  - Suppressed immunity could cause **infection and/or cancer?**
  - In fact: Post-transplantation risk with Tac inducing PTLD :
    - children: 10~20% (5 y)~**
      - may be 30-50% (20 y)**
    - adult : 1~5% (5y), 15%(13y:cyclosporin)**
- more on the text:

## Cancer Risk in rat carcinogenicity study (%)



\*\* : p=0.008    \*\*\* : p=0.00053    \*\*\*\* : p<<0.00001 compared with vehicle; Analyzed by JIP using the SBA data; Industry claims 0.03% safe comparing with “sham”; inappropriate according to the ICH guideline

Fig1 Concentration (logC) of tacrolimus, excess cancer and lymphoma risk (24 months mice carcinogenicity study)



# Summary of tacrolimus

- Concentration for transplantation is 10~20 ng/mL: same level as the mice carcinogenic level.
- **Maximum clinical blood level** of tacrolimus treated as ointment is estimated about 2 ng/mL. It **is only one third of the mice carcinogenic level.**
- **ICH guidance** recommended that maximum clinical level should be **25 times less** than the least carcinogenic level **in the rodent based on AUC** (or 150 times less than that mg/kg base.
- So animal carcinogenicity test show that it's approval **violates the ICH guidelines.**
- We have **no experience** using tacrolimus ointment **in enough periods** for inducing cancer. But **if you carefully analyze the animal carcinogenicity study, you can predict it's cancer risk with significant extent.**
- **At least the results are excellent warnings.**