



Surveillance for survivors of Childhood Cancer

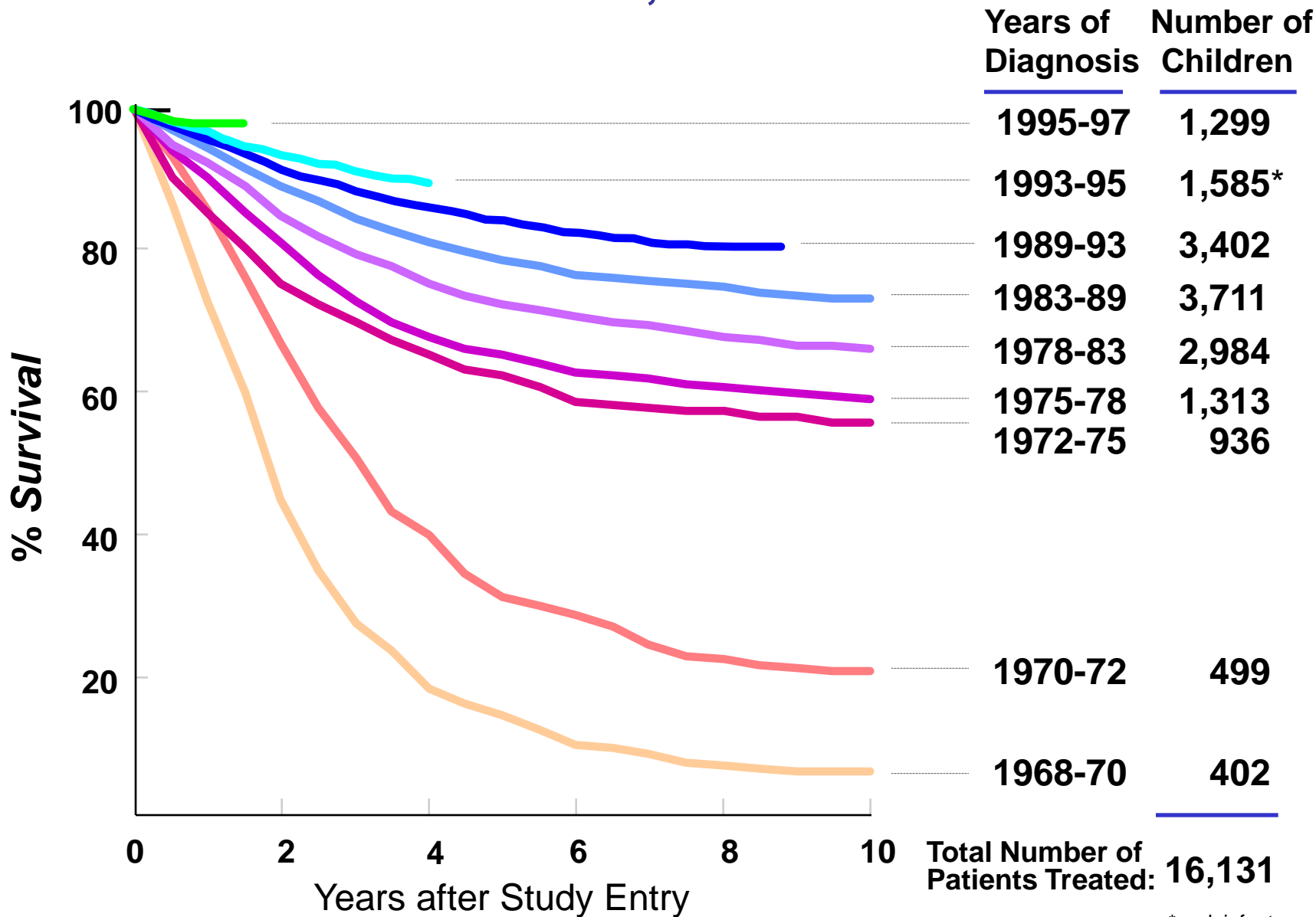
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Survival Rate

- Over the last 30 years there has been a continuous improvement in cure rate for childhood cancer

Survival of CCG Patients with Acute Lymphoblastic Leukemia, 1968-1997



Chances of Surviving Cancer if Diagnosed before Age 20?



- 80-85%



What is a Survivor?

- There are many definitions
- For late effects:
 - Someone who has survived for at least 5 years since the last evidence of disease and at least 2 years since stopping treatment



Late Effects

- Late effects are complications, disabilities or adverse outcomes that are persistent and are the result of the disease process, the treatment or both.
- At least 65% of childhood cancer survivors will suffer from at least one late effect although most are mild
- 25% will have a severe or life threatening late effect
- Many of these late effects do not become apparent until many years later



Purpose of surveillance for Survivors of Childhood Cancer

- Prevention of Late Effects
 - Eg Treatment with growth hormone to prevent short stature
- Early Detection of Late Effects
 - Eg Breast and brain tumour surveillance
- Treatment
 - Eg Thyroid hormone replacement
- Research
 - Eg New drugs and unknown effects of old drugs
- Counselling
 - Eg Infertility
- Education
 - Eg Patients and health care workers



Focus on 4 Late Effects

- Cardiac Toxicity
- Hypothyroidism
- Fertility
- Breast Cancer



Cardiac Toxicity



- Cause of death in 5 year survivors of childhood cancer
 - Recurrence of primary cancer
 - Secondary cancer
 - Heart and CVS disease



Cardiotoxicity

Causes of cardiotoxicity

- Anthracyclines
- Other Chemotherapy
- Mediastinal and Neck Irradiation

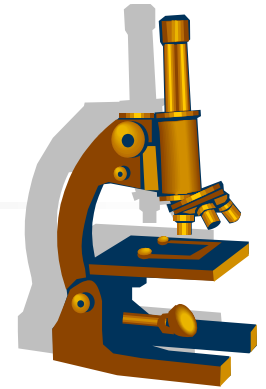


Types of Cardiac Problems seen in survivors

- Cardiomyopathy
- Pericarditis
- Congestive cardiac failure
- Valvular heart disease
- Premature coronary artery disease
- Atherosclerosis in large arteries in the neck

Anthracycline Induced Cardiomyopathy

- Myocyte injury mediated by generation of free radicals and incorporation of iron
- Cardiac myocytes more susceptible because of highly oxidative metabolism
- Results in loss of myofibrils, and cytoplasmic vacuolisation





Anthracycline cardiomyopathy

- Acute – transient arrhythmia, pericarditis
- Chronic – within 1 year.
- Late onset – years to decades later

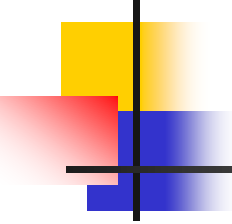
- Chronic and late onset are dose dependent
- Risk factors
 - Age <5 years at treatment
 - Female
 - Black race
 - Combination with other chemotherapy eg Cyclo
 - Mediastinal radiation
 - Higher dose of anthracyclines**



What dose of Anthracycline is safe?



- Higher cumulative doses are associated with higher incidence of subclinical and clinical dysfunction.
- Patients with ALL receiving doses of 90-270 mg /m²
 - 23% had subclinical dysfunction.
 - Only those with >240mg/m² showed progressive decrease in function (Sorenson 2003)
- 75% of children who received a median dose of 330mg/m² had progressive decrease in LVF (Lipshultz 1991)
- Long term consequences of subclinical dysfunction are not known and long term research needs to be done



Radiation Induced Cardiovascular Disease

- Radiation to the chest can cause
 - Constrictive pericarditis
 - Cardiomyopathy
 - Valvular heart disease
 - Coronary heart disease
 - Conduction defects
- Radiation to the neck can cause
 - Atherosclerosis in the carotids and subsequent stroke



What Surveillance is Appropriate?

- Assess cardiac risk
 - Cumulative Dose of anthracyclines
 - Age at treatment
 - Other chemotherapy eg high dose cyclophosphamide
 - Radiation to chest or neck
 - Other Cardiac risk factors
 - Pre-existing cardiac disease, smoking, pregnancy, obesity, rapid growth, smoking



Monitoring for Cardiac Toxicity

- No Risk
 - No anthracyclines or radiation
 - Low Risk
 - Anthracyclines < 250mg/m²
 - No radiation
 - Over 5years old at treatment
 - Moderate Risk
 - Radiation to chest or neck
 - Anthracyclines > 250mg/m², < 400mg/m²
 - Age <5 with any anthracyclines
 - High Risk
 - Anthracyclines plus radiation to chest
 - Anthracyclines > 400mg/m²
 - Pre existing cardiac disease plus anthracyclines
- No Risk
 - No surveillance
 - Low Risk
 - ECG, Echo q 2-3 years until after puberty.
 - ?every 5-10 years thereafter
 - Moderate Risk
 - ECG, Echo every year until after puberty and every 2-5 years thereafter
 - Doppler ultrasound of neck for radiation
 - High Risk
 - ECG, Echo every year
 - Doppler ultrasound of neck



Counseling and Treatment of cancer associated cardiac disease

- Counseling – Weight, exercise, smoking
- Monitor blood pressure, glucose, lipids
- Pregnancy increases cardiac workload.
 - May need extra monitoring during pregnancy
- Treatment of subclinical heart disease is controversial
 - Use of ACE inhibitors or beta blockers not established
 - For deteriorating values -Monitoring by a cardiologist recommended
- Treatment of clinical heart disease requires specialized cardiac care
 - Developing cancer cardiac care centre at VGH
- We do not yet know the impact of anthracyclines and radiation on the aging heart



Hypothyroidism

- Thyroid gland is extremely sensitive to effects of radiation
 - Hypothyroidism
 - Thyroid cancer
- 1000cGy results in >30% incidence of hypothyroidism
 - If brain is not irradiated TSH will usually increase
 - If brain is irradiated TSH may not increase
- Radiation doses as low as 30cGy increase the risk of thyroid cancer. Tumours are usually papillary and have an excellent prognosis if treated early.
 - Highest risk
 - Females
 - Young age at radiation exposure
 - Dose of radiation (increased risk up to 3000cGy and then risk decreases)
 - Duration of TSH increase



Thyroid Monitoring and Treatment

- If had Radiation to thyroid and/or brain
 - Annual history and examination of thyroid
 - Annual T4, TSH
 - ?Thyroid ultrasound. Efficacy not established but usually recommended.
- Treatment
 - Hypothyroidism
 - Thyroxine
 - Thyroid tumour
 - Thyroidectomy +/- Radioactive iodine

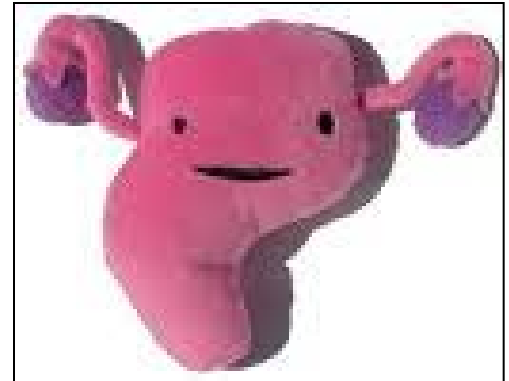


Radiation damage

- The ovaries are very sensitive to the effects of radiation to
 - Abdomen, pelvis, TBI or craniospinal
 - ? Diagnostic radiation
- Oocytes have LD50 of <200cGy. Effect on fertility depends on
 - Dose received by ovaries
 - Number of follicles present at time of treatment
 - May develop
 - Acute ovarian failure
 - Premature menopause
- Cranial radiation
 - High dose (>2400cGy) can cause delayed puberty or absent menses
 - Low dose (<2400cGy) can cause premature puberty

Adverse Effects of Radiation - to the Uterus

- Uterus may be damaged by doses $>1000\text{cGy}$
 - Decreased uterine vasculature
 - Decreased muscular elasticity
 - Decreased growth and positional abnormalities for fetus
 - Cervical incompetence and pre-term birth





Gonadotoxic chemotherapeutic agents

- Highest risk
 - Alkylating agents
 - Procarbazine
 - Cyclophosphamide
 - Ifosfamide
 - Nitrosoureas (CCNU, BCNU)
 - Melphalan
 - Busulphan
- Moderate risk
 - Platinum agents
 - Cytarabine
 - Vinblastine
 - Anthracyclines
 - Associated with congestive heart failure during pregnancy

Risk higher in older women

How can we Monitor Ovarian Reserve?

- Menstrual History and FSH – not very useful
 - By the time FSH increases ovarian failure is imminent
- Antral follicle count is useful but very labour intensive
- Anti Mullerian Hormone
 - Granulosa cells- cycle independent
 - Reflects total primordial follicle numbers
 - Declines within 5 years of menopause
 - If have low AMH will have poor ovarian response
 - Only available at private labs in BC and very expensive.
-





Fertility Preservation - Females

- Ovarian Shielding prior to XRT
- Ovarian transposition
 - Into abdomen
 - To other sites (Heterotopic)
- GnRH agonists? (Huser 2008)

Fertility Preservation - Females

- Embryo cryopreservation
 - Well established, millions of babies born
 - BUT – need a partner so not suitable for most of our patients
- Oocyte Cryopreservation (after hormone stimulation)
 - Successful, approx 2000 live births
 - BUT- takes 2-3 weeks of hormone treatment

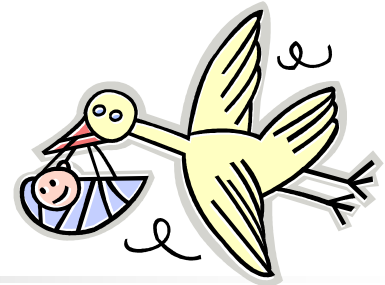




Fertility Preservation- Females

- In Vitro Maturation (IVM) - Oocyte Cryopreservation (unstimulated) followed by in vitro maturation and vitrification.
 - Small numbers fertilized and cryopreserved. Still experimental
- Cryopreservation of ovarian tissue (ovarian cortical strips). Re-implanted later
 - 6 live births
 - OK for pre pubertal girls
 - Risk of damage to ovary and 2 procedures
 - Risk of transplanting malignant tissue

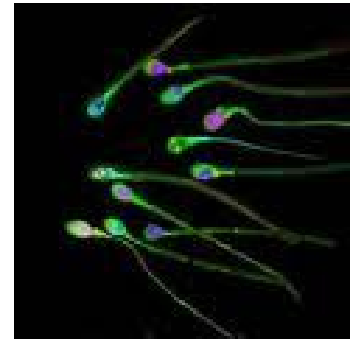
Alternatives



- Cryopreserve oocytes or embryos in the window prior to premature menopause if high risk
- Adoption
- Surrogate Mother if ovaries OK but uterus damaged
- Donated oocytes if ovaries damaged but uterus OK

Normal Testicular Function

- Functions
- To produce spermatazoa
 - Spermatogenic cells
 - Sertoli (nurse) cells
 - 3 billion sperm / month, 100/heart beat !!
- To produce testosterone
 - Leydig cells





Adverse Effects of Radiation to the Testis

- Testicular radiation
 - For leukemic infiltration
 - TBI
- Testis is very sensitive to radiation
 - 100-120cGy can impair spermatogenesis
 - 400cGy can cause permanent azoospermia
 - Residual sperm may have increase fragmentation
 - May have some recovery over a few years
- Leydig cells are more resistant
 - Dysfunction
 - > 2000cGy in prepubertal boys
 - >3000cGy in mature males



Adverse Effects of radiation to the Hypothalamus-pituitary-testis axis

- Low dose cranial radiation (<2400)
 - less likely to cause precocious puberty in boys than girls
- High dose cranial radiation (>2400cGy)
 - At risk for Hypogonadotropic hypogonadism – risk increases with dose
 - Treatment – testosterone replacement



Adverse Effects of Chemotherapy on the Testis

- Germinal epithelium is very sensitive to chemotherapy- especially alkylating agents. More sensitive than the ovary
 - Recovery less likely after chemotherapy than XRT
- Leydig cells rarely affected (high cumulative doses only)
- Follow up of teenage boys treated with a combination of procarbazine and chlorambucil showed >50% had severe gonadotoxicity with small testicular volumes, High gonadotropin levels and low or absent sperm counts (Mackie 1996)
- ABVD (or similar regimens) now used for low stage HD in males.



Gonadotoxic chemotherapy drugs

- Highest risk

- Alkylating agents
 - Procarbazine
 - Cyclophosphamide
 - Ifosfamide
 - Nitrosoureas (CCNU, BCNU)
 - Melphalan
 - Busulphan

- Moderate risk

- Platinum agents
- Cytarabine
- Vinblastine



Adverse effects of surgery

- Orchiectomy – for testicular cancer
- Radical retroperitoneal lymph node dissection
 - dry ejaculation or ED
- Radical prostatectomy
 - ED (30 -80%)

Fertility Preservation - males

- Sperm Banking
 - Well established, successful
 - Must be Tanner 4-5
 - Masturbation
 - Penile vibratory stimulation
 - Rectal electrostimulation
 - Often low sperm count at diagnosis
- Should be offered to all male patients > Tanner stage 3
- 3 local fertility centres
- Currently developing protocol and guidelines



Roadblocks to Sperm banking

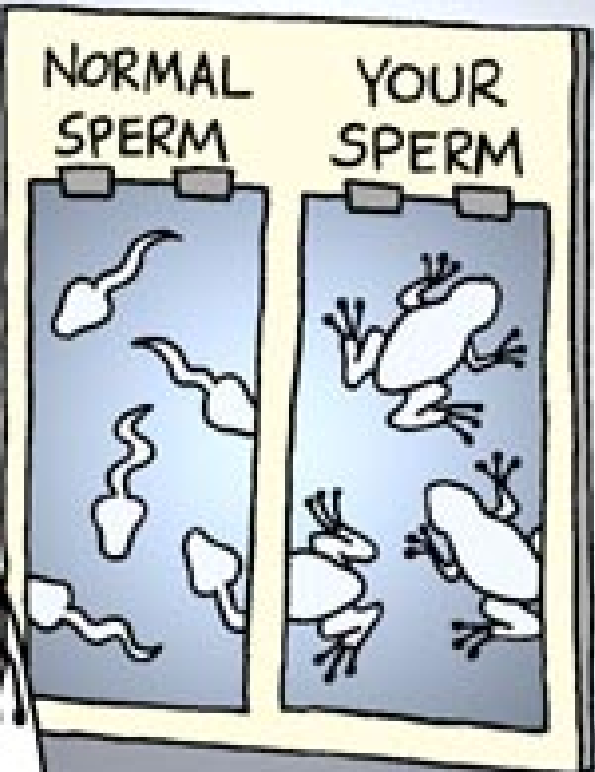
- Cost
- Time
- Life threatening complications
- Access to cryopreservation
- Biases
- Patient education
- Caregiver education
- Patient refusal

- Need a team approach
- Protocols that work
- Facilities that are child/teen friendly

- **Only 17.8% of newly diagnosed AYA patients cryopreserve sperm (Neal, Cancer 2007)**



I take it
you haven't
had sex
for a while



whyatt

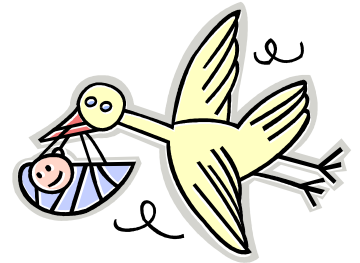


Surgical methods

- Surgical sperm retrieval
 - For patients who are not able to produce a semen sample by other means
 - Involves a small incision in the scrotum and extraction of sperm from the epididymis or testis
- Testicular tissue cryopreservation
 - Remove a small part of the testis and cryopreserve and later re-implant
 - No reports of success so far

Use of cryopreserved sperm

- Depends on number and quality of sperm
- With good quantity and quality
 - Intra uterine insemination is 36.5% effective
- With limited quantity or quality
 - IVF or ICSI is 54.5% effective(Neal, Cancer 2007)
- Alternatives
 - Adoption
 - Sperm donor



Ethics of Oncofertility



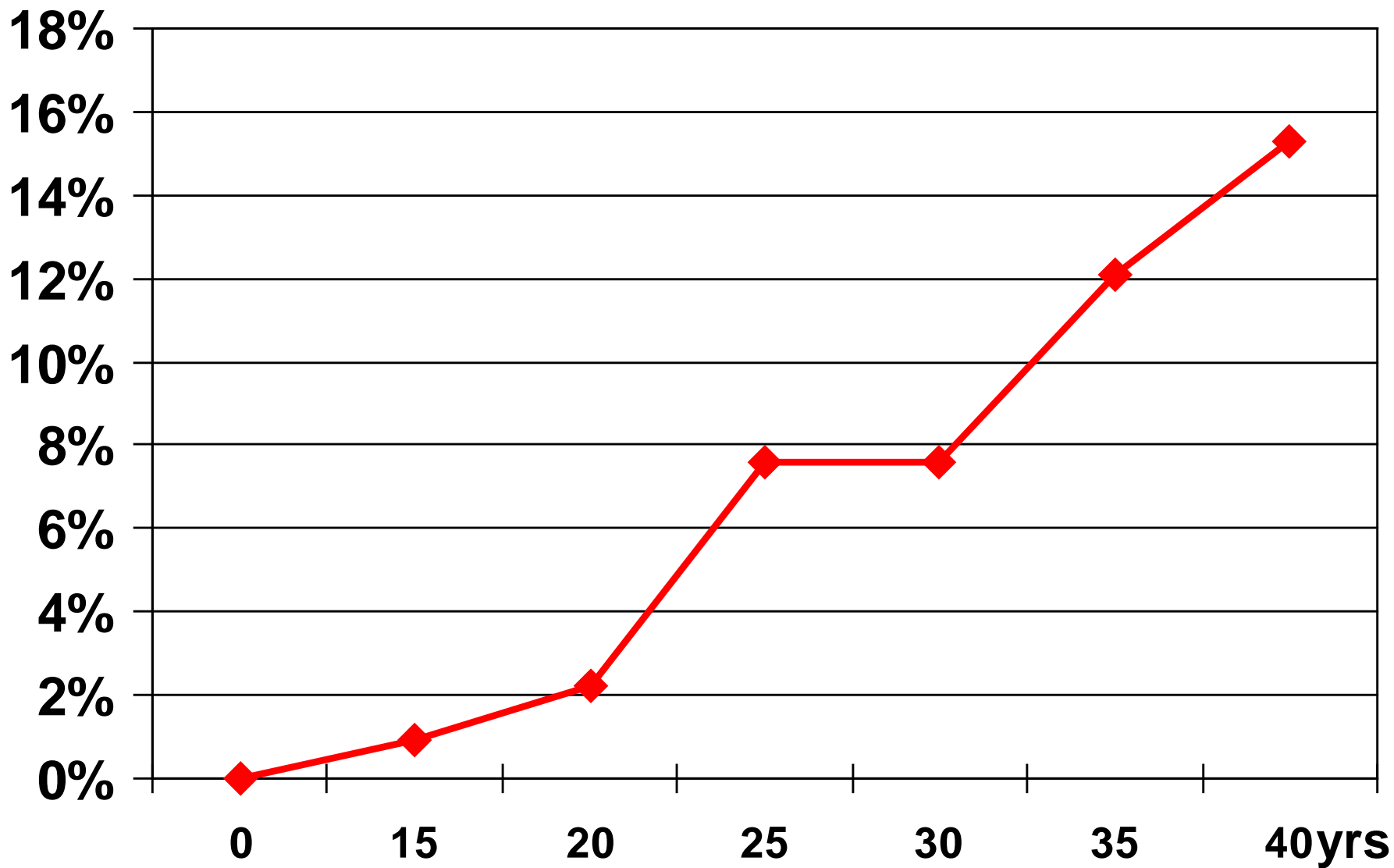
- Informed choice for young patients
 - Is it the child's choice or the parents?
- Consideration of sperm donor for embryo freezing for young adults
- Pressure to create embryo with current partner
- Assisted Human Reproductive act
 - Sperm or ovum from under age 18 is only allowed for the purpose of creating a human being that is reasonably believed will be raised by the individual
- Concern regarding premature menopause may encourage pregnancy too early



Secondary Breast cancer

- Exposure of the breast to radiation increases the risk of breast cancer
- The risk is highest when radiation given during breast development at puberty
- Female patients with Hodgkins disease treated with mediastinal radiation have the highest risk
- Follow up of a cohort of females treated for Hodgkins Disease under age 16.
 - Probability of breast cancer by 30 years from diagnosis = 28%

B.C. Cumulative Risk of Breast Cancer



Reported Incidence of Secondary Breast Cancer Following Female Childhood HD

Report	# of cases	%	Cumulative @ 25yrs
B.C. Data	6/111	5.4	7.6%
Nordic (Sankila 1996)	16/670	2.4	10%
UK (Taylor 2006)	16/383	4.2	9.9%
Dutch (van Leeuwen 2000)	27/544	5.0	10%
Late Effects SG (Bhatia 2003)	29/480	6.0	14%



Monitoring for Breast Cancer

- Patient awareness
 - Patients need to be informed of their risk
 - In the UK it is mandatory to recall patients exposed to breast irradiation and offer them screening program
 - In BC funding for such a program has not been successful. Most of our survivors are not being screened and are not aware of their risk
- Screening
 - Annual physical exam
 - Mammography- annual
 - MRI (where available) – annual
- Treatment is much more likely to be successful if detected early