ISTITUTO PER LO STUDIO
E LA PREVENZIONE ONCOLOGICA

Pregnancy-associated breast cancer

Collaboration among cancer registries is needed to overcome the limit of small numbers

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Grell 2012

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Pregnancy-associated breast cancer

- Breast cancer (BC) diagnosed within the pregnancy or during the first year after delivery (Petrek JA, 2004) but a longer period after delivery is also considered (Johansson CCC 2012, Pilwskie 2012, Schedin 2006)

The role of pregnancy in breast cancer

- Overall pregnancy reduces the life-time risk of developing a breast cancer (MacMahon JNCI 1973, Rosner, AmJEpidemiol 1994, Albrektsen, Epidemiology 1994)
- Crossover effect: before the age of 40 parous women were at higher risk of BC than nulliparous, after the 40 the risk reverses (Janerik&Hoff, AmJEpidemiol1982).
- There is a transiet increase in BC risk following pregnancy, however because most cancers are diagnoses in older women the cumulative effect of pregnancy is to lower the risk.

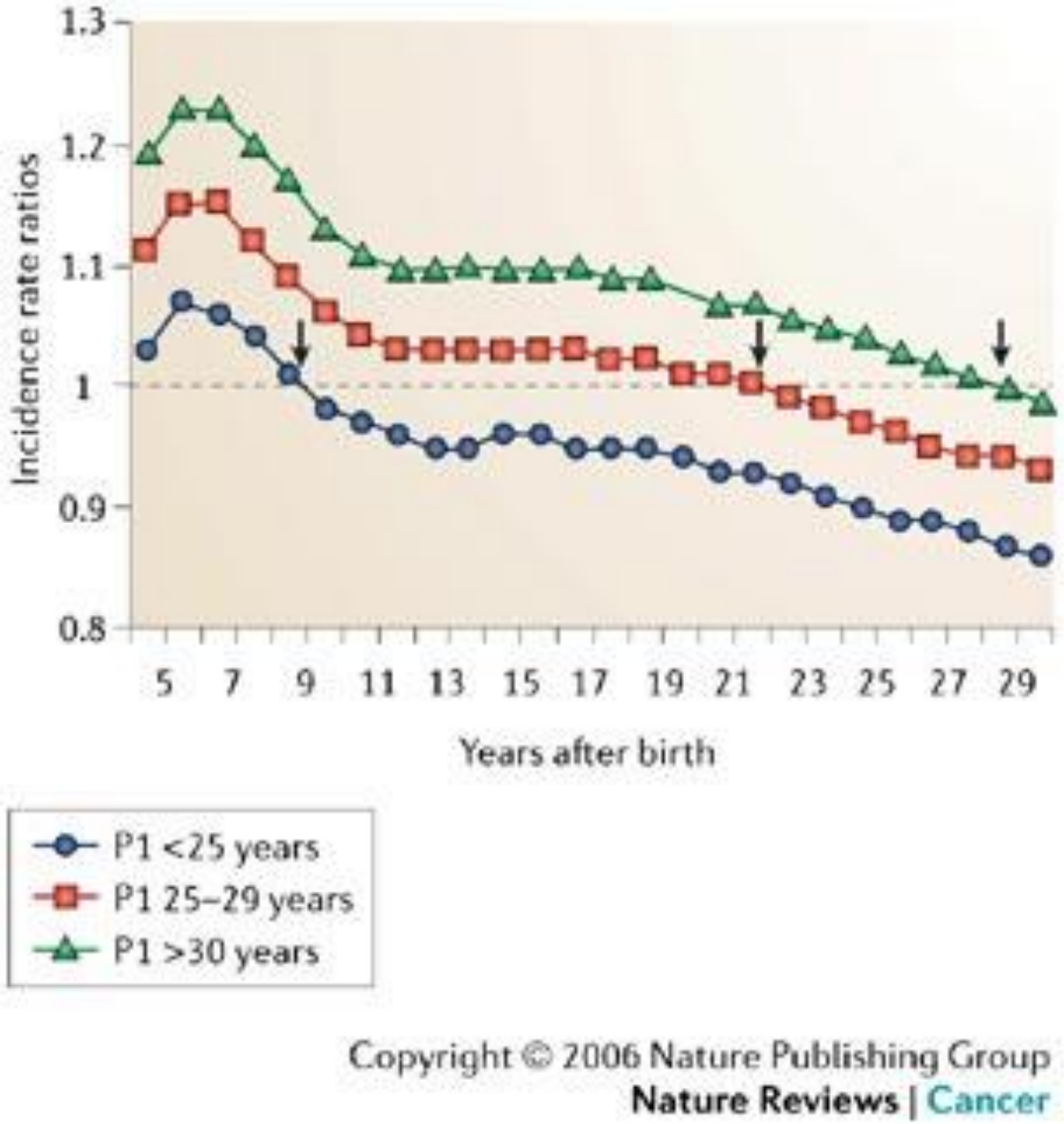
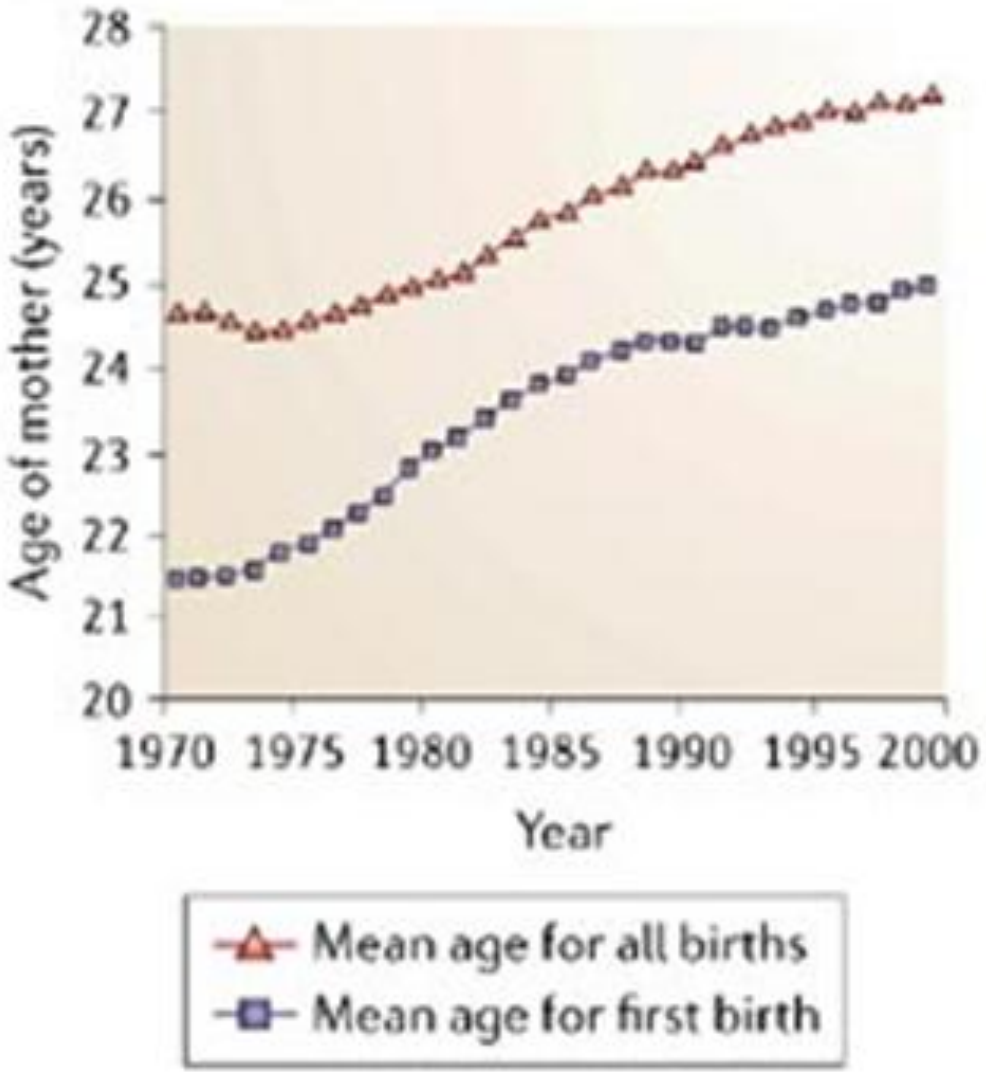


Figure 1 | **Evidence for a transient increase in breast cancer risk following pregnancy.** This figure shows the predicted incidence-rate ratio of breast cancer for women of parity according to time since first birth (P1), in subgroups of 'age at first birth' (for nulliparous women, the relative-rate ratio = 1.0). In this cohort of 22,890 women with breast cancer, a transient increase in risk is seen up to 10-years post-pregnancy (see REF. 9). In young mothers, the crossover to protection occurs approximately 10 years after first pregnancy (indicated by the arrow). For mothers aged 25–29 years, crossover to protection occured around 22 years after pregnancy (indicated by the arrow), and for mothers 30 years and older, the crossover occured approximately 30 years after pregnancy (indicated by the arrow). Data compiled from incidence-rate ratio charts provided by G. Albrektsen, University of Bergen, Norway using a no-interaction model.

Schedin *Nature Reviews Cancer* **6**, 281–291 (April 2006) | doi:10.1038/nrc1839

nature REVIEWS CANCER



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Pregnancy-associated breast cancer

- Pregnancy may:
- cause a delay in diagnosis
  - due to increase in breast density during pregnancy and breastfeeding making clinical examination and mammography more difficult to interpret (more advanced stage at diagnosis)

- have a promotional effect (of gestational hormones)
  - oestrogen, ILGF1, progesterone are intimately associated with BC aetiology and progression, so they may be responsible for more aggressive cancers

Data from literature show **conflicting results** on PABC biology and prognosis

- Worse prognosis due to worse stage at diagnosis, more inflammatory cancers, G3, high Ki, ER- and PgR – (Petrek, 2004)
- Worse pathologic features, but after adjustment same survival (Murphy 2011, Daniilidis, EurJGynaecol Oncol 2010)
- Worse prognosis (death and recurrence) also after adjusting for stage (Ali, 2012, Moreira SaoPauloMedJ 2010)

- PABC have an higher mortality than non-PABC (Johansson 2011)
- Similar prognosis between PABC and not-PABC (Beadle, 2012, Halaska, 2009)

- Similar prognosis between PABC diagnosed during pregnancy and PABC diagnosed within 1 year (Beadle 2009)
- PABC diagnosed during lactation worse prognosis than PABC during pregnancy (Stensheim JClinOncol2009)

Objective of the present study

Comparing the characteristics of PABC and non-PABC in the Tuscany Cancer Registry, Italy

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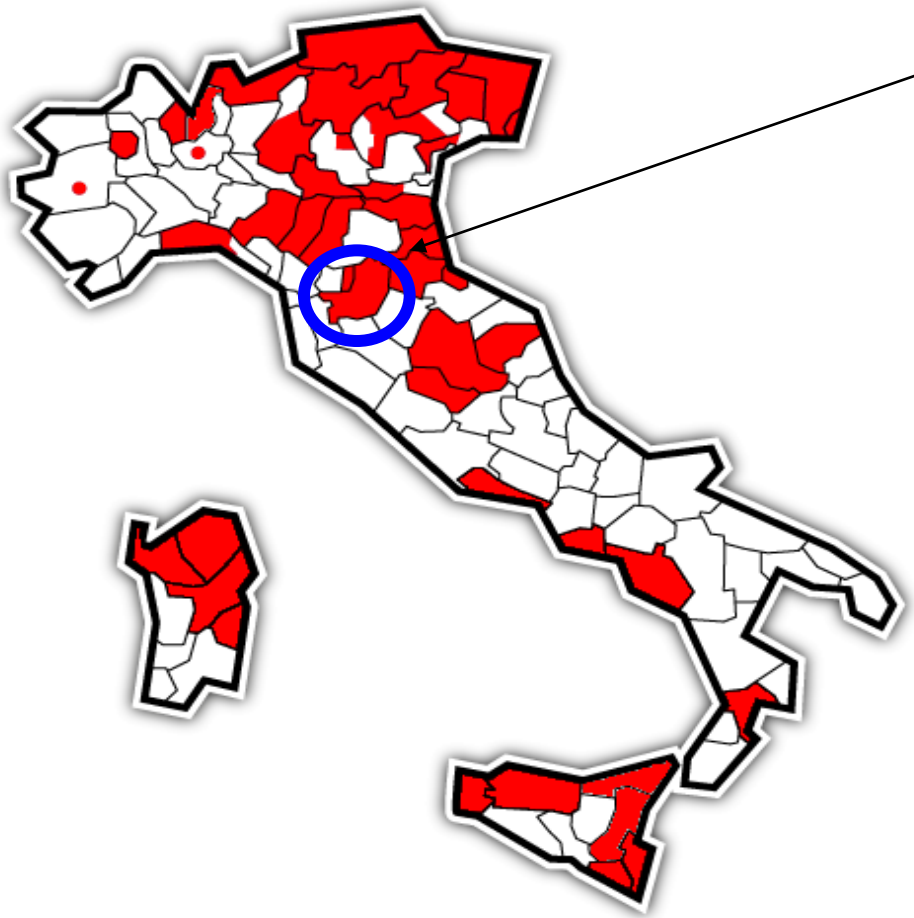
Italian network of cancer registries AIRTUM

(www.registri-tumori.it) 24.000.000

Tuscany Cancer Registry



Active since 1985

Population: 1,200,000 inhabitants

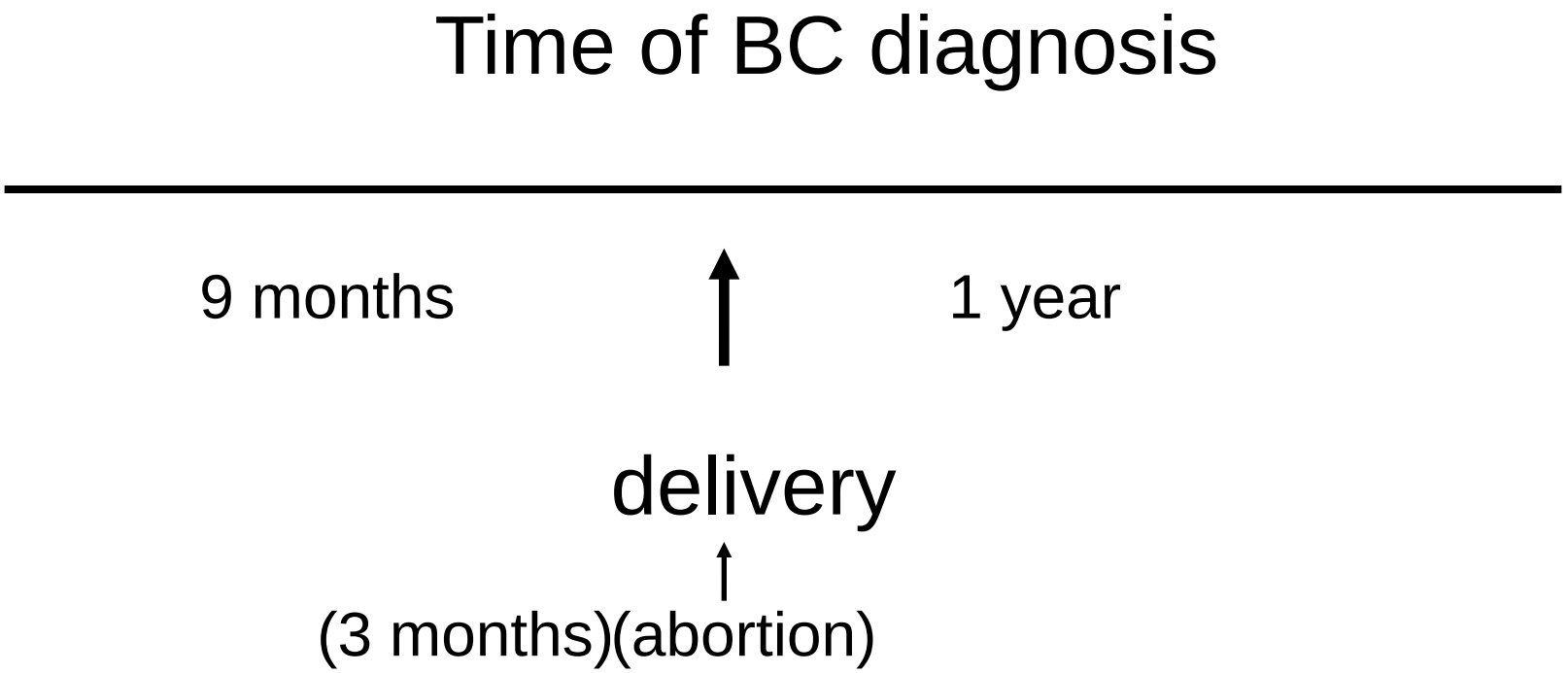
Methods

- Tuscany cancer registry: all BC diagnosed in women <=45 years from 2000 to 2006

  these cases were linked with

- Pregnancy related hospital admissions (public or private but operating within the national health service) in and outside the registry area (ICD-9 codes 630-670)
  - 630-633 ectopic and molar pregnancy
  - 634-639 other pregnancy with abortive outcome
  - 640-649 complications mainly related to pregnancy
  - 650-659 normal deliver, etc
  - 660-669 complications occurring mainly in the course of labour or delivery
  - 670-677 complication of the puerperium
  - 678-679 other maternal and fetal complications

PABC were defined as BC diagnosed from 9 months before to 1 year after a delivery (Petrek JA, 2004) , or from three months before an admission for miscarriage/abortion



Method

- We sampled 4 non-PABC (controls) for each PABC matching for age (+/- 4 years) and year of incidence (+/- 1 year)
    - Stage I vs II+
    - Grading well-intermediate vs poor
    - ER+ vs ER-
    - PgR+ vs PgR-
    - Ki<14 vs Ki>14
    - Cerb 0-1 vs 2-3
- Logistic regression for matched data

Results

During 2000-2006 there were 732 invasive BC diagnosed in women aged <=45 years

- PABC
- 25 (3.4%)
- mean age 36.4, median 36.6
- range 29.1-44.0

- Non-PABC
- 707 (96.6%)
- mean age 40.7
- median 41.7
- range 22.5-45.9

Results (25 PABC vs 100 non-PABC)

		OR*		p
Stage	I	1		
	II+	1.29		0.66
	n.a.	1.54		0.56
Grading	Well / Intermediate	1		
	Poor	2.87		0.057
	Unknown	1.47		0.57

*ORadjusted for age and year of incidence

Results (25 PABC vs 100 non-PABC)

		OR*		p
ER	+	1		
	-	1.80		0.28
	n.a.	1.97		0.23
PgR	+	1		
	-	1.90		0.27
	n.a.	2.06		0.22

*ORadjusted for age and year of incidence

Results (25 PABC vs 100 non-PABC)

		OR*		p
Ki	Negative (<14)	1		
	Positive (>14)	3.91		0.09
	Unknown	4.42		0.09
Cerb	0-1	1		
	2-3	1.92		0.35
	Unknown	3.81		0.03

*ORadjusted for age and year of incidence

Results (25 PABC vs 100 non-PABC)

Goldrish 2011

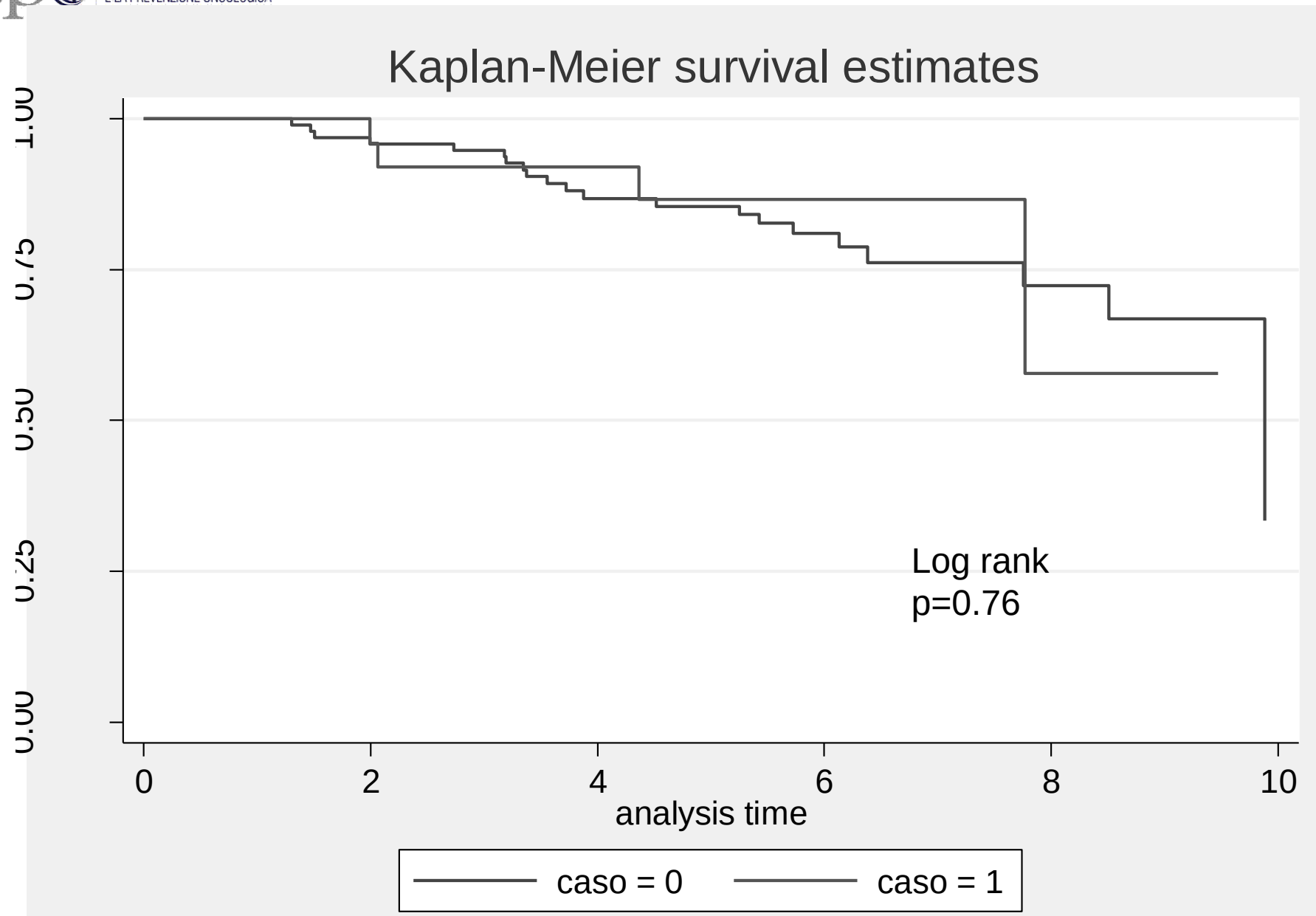
	OR*		
Luminal A	1		
Luminal B her2+	2.5		0.53
Luminal B her2-	2.6		0.47
Triple -	6.4		0.17
Her2 type	10.8		0.08
Not defined	11.9		0.05

*ORadjusted for age and year of incidence

Results(25 PABC vs 100 non-PABC)

		OR**	p
Stage	I	1	
	II+	1.25	0.74
	n.a.	1.87	0.60
Grading	Well /Inter	1	
	Poor	1.87	0.57
	Unknown	0.58	0.57
ER	+	1	
	-	0.63	0.69
	n.a.	2.2	0.57
PgR	+	1	
	-	2.05	0.54
	n.a.		
Ki	-	1	
	+	2.85	0.27
	n.a.	1.19	0.91
Cerb	0-1	1	
	2-3	1.27	0.26
	n.a.	4.26	0.95

**Oradjusted for al l the variables


Kaplan-Meier survival estimates
1.00
0.75
0.50
0.25
0.00
0
2
4
6
8
10
analysis time
Log rank
p=0.76
caso = 0
caso = 1

Conclusion-1

- PABC did not show a different stage at diagnosis than non-PABC (presumably no delay in diagnosis)
- There was a slightly worse biological pattern (worse grading, higher Ki, more HER2 type), no differences in the multivariable analysis
- Similar OS between PABC and non-PABC that means no (other) strong biological or clinical significative differences

Conclusion-1

- Weakness:
  - missing data on biological markers (quite a lot ~ 20%)
  - Possibly PABC among controls
    - Completely private clinic were not included (very few)
    - Deliveries at home were not included (very few)
  - …..
- Major weakness:
  - The small numbers hampered a comprehensive evaluation

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Let's put our data together!

- This issue is relevant and its frequency is increasing and the case-series in the literature are rather small. Grell could contribute with reliable epidemiological data

- Who is interested in a collaborative study please contact me:
- e.crocetti@ispo.toscana.it

- We will define together the protocol