Institut de cancérologie
GUSTAVE ROUSSY
VILLEJUIF - www.igr.fr

Cancer du sein chez la femme jeune: effets secondaires et traitements systémiques (hors hormonothérapie)

Suzette Delaloge
Institut Gustave Roussy, Villejuif

Conflits d'intérêt – S Delaloge

	Consulting/ expert	Conferences/ formations	Research grants /clinical trials	Stock options	Patent
Abraxis	x				
Amgen		x	x		
Astra Zeneca		x	x		
Bayer	x				
BMS			x		
Exonhit			x		x
GE		x	x		
GSK	x	x	x		
Merck			x		
Novartis	x	x	x		
Pierre Fabre		x	x		

Deux types de risques à long terme

- Risques vitaux
- Altérations à long terme de la qualité de vie

Deux types de risques à long terme

- Risques vitaux
- Altérations à long terme de la qualité de vie

Risques vitaux

- Y a-t-il un sur-risque de mortalité hors cancer du sein?
- Y a-t-il un sur-risque de pathologies menaçant le pronostic vital?

  – Difficile de distinguer ce qui relève des traitements systémiques versus radiothérapie versus contexte génétique versus l'ensemble….

CAUSE-SPECIFIC MORTALITY IN LONG-TERM SURVIVORS OF BREAST CANCER: A 25-YEAR FOLLOW-UP STUDY

MAARTJE J. HOONING, M.D.,* BERTHE M. P. ALEMAN, M.D.,† AGNES J. M. VAN ROSMALEN,* MARIANNE A. KUENEN,* JAN G. M. KLIJN, M.D., PH.D.,‡ AND FLORA E. VAN LEEUWEN, PH.D.*

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 4, pp. 1081–1091, 2006

Table 2. Causes of death in the Dutch late effects BC study

Cause	ICD-9	O (%)	SMR (95% CI)
Infectious diseases	1–139	8 (0.2)	0.96 (0.42–1.90)
Breast cancer (including CLBC*)	174	3163 (76.0)	39.4 (38.0–40.8)
Second malignancies (excluding CLBC*)	140–208, 174 excluded	309 (7.4)	1.16 (1.03–1.29)
Endocrine, nutritional, and metabolic diseases	240–279	9 (0.2)	0.22 (0.10–0.42)
Mental disorders	290–319	18 (0.4)	0.83 (0.49–1.32)
Diseases of the nervous system and sense organs	320–389	14 (0.3)	0.64 (0.35–1.07)
Diseases of the circulatory system	410–459	394 (9.5)	0.96 (0.86–1.05)
Cardiovascular disease	410–414; 420–429	269	1.04 (0.92–1.17)
Cerebrovascular accident	430–438	92	0.84 (0.68–1.03)
Diseases of the respiratory system	460–519	62 (1.5)	0.95 (0.73–1.22)
Diseases of the digestive system	520–579	35 (0.8)	0.86 (0.60–1.19)
Diseases of the genitourinary system	580–629	8 (0.2)	0.42 (0.18–0.83)
Miscellaneous diseases†		7 (0.2)	
III-defined conditions and unknown	780–799	100 (2.4)	2.70 (2.20–3.29)
External causes of injury and poisoning	800–999	33 (0.8)	1.04 (0.71–1.46)
Complications of treatment		6	
All causes		4160	3.88 (3.76–4.00)

Mortalité par seconds cancers, tous âges confondus

Risques absolus

Table 3. Mortality from second malignancies

Cause of death	O	E	SMR	95% CI	AER*
All second malignancies (including CLBC)	493	347.3	1.42	1.30–1.55	16.6
Esophagus	12	5.6	2.14	1.11–3.74	0.7
Stomach	19	16.9	1.12	0.69–1.76	0.2
Colon, rectum	47	44.8	1.05	0.77–1.40	0.3
Lung	58	33.7	1.72	1.31–2.23	2.8
Contralateral breast	184	80.3	2.29	1.97–2.65	11.8
Soft tissue	5	2.0	2.50	0.81–5.83	0.3
Melanoma	7	3.6	1.94	0.78–4.01	0.4
Cervix	13	7.2	1.81	0.96–3.09	0.7
Uterus	7	8.8	0.80	0.32–1.64	−0.2
Ovary	46	26.5	1.74	1.27–2.32	2.2
Non-Hodgkin's lymphoma	12	10.1	1.19	0.61–2.08	0.2
Leukemia	16	9.1	1.76	1.01–2.86	0.8

Sur-risque de décès selon le recul et causes, tous âges confondus

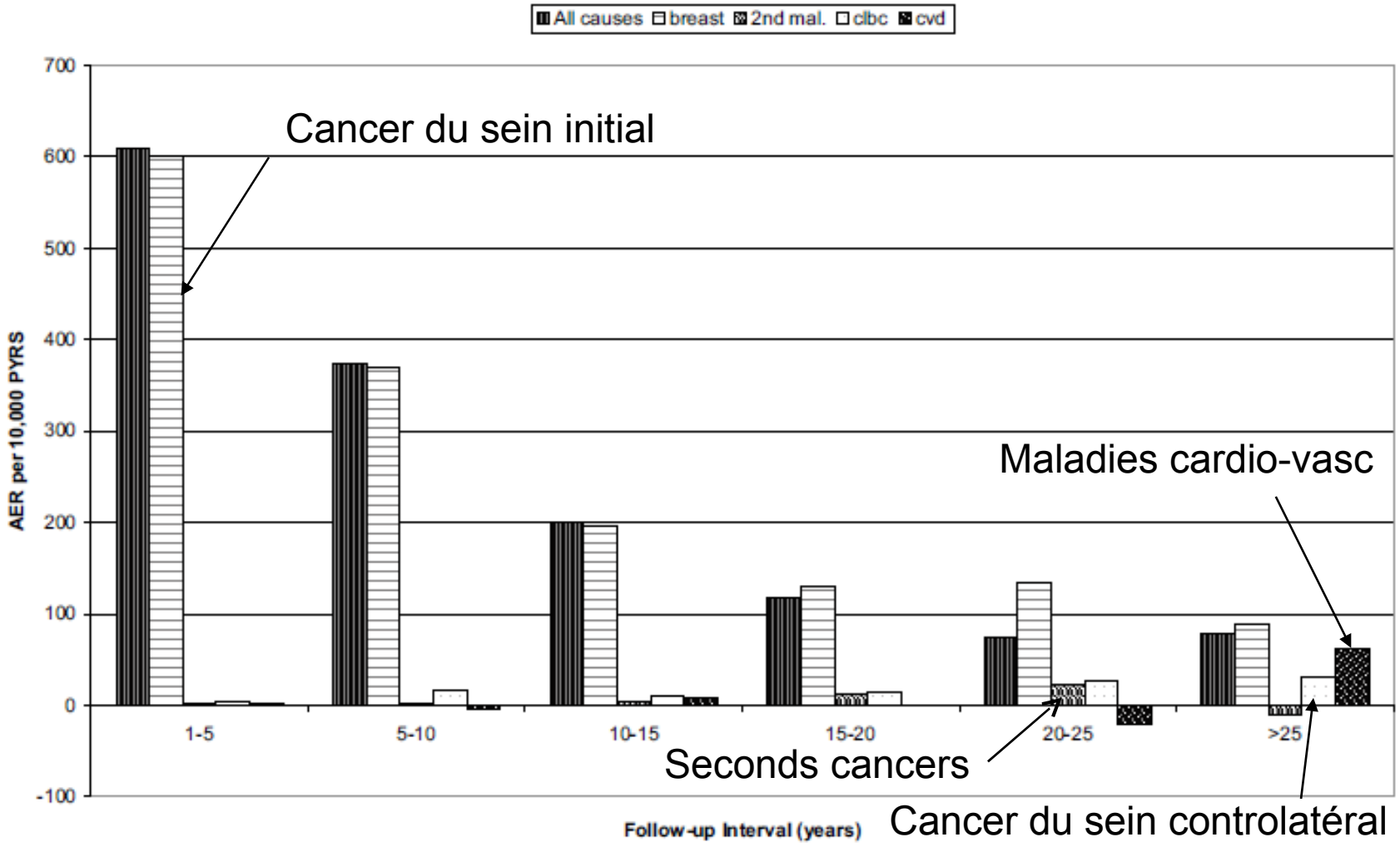


Fig. 2. Absolute excess risk of death from various disease categories over time, in comparison with the general population. 2nd mal = second nonbreast malignancies; clbc = contralateral breast cancer; cvd = cardiovascular disease; AER = absolute excess risk; PYRS = person-years.

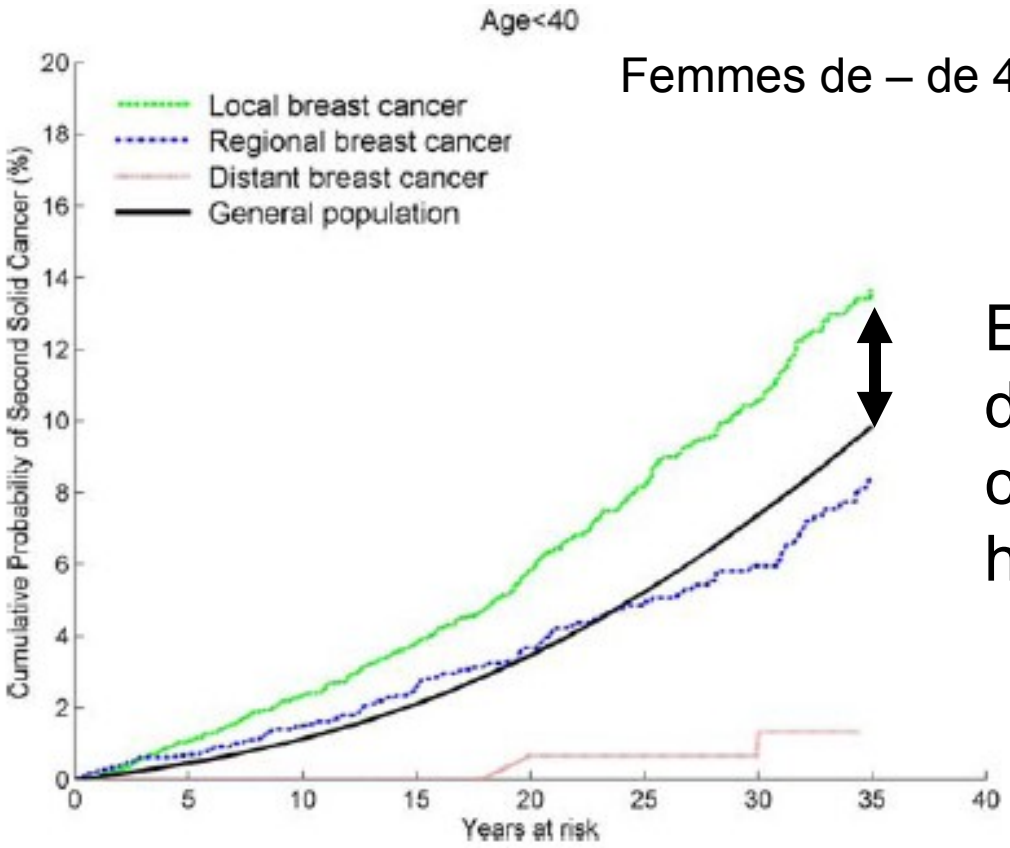
Sur-risque de décès selon l'âge par cause

	Solid tumors, excl. breast cancer				Leukemia, myeloma, lymphoma			
	O	SMR	95% CI	AER*	O	SMR	95% CI	AER*
Overall	277	1.15	1.02–1.29	4.2	32	1.18	0.81–1.67	0.6
Age at diagnosis								
<35 years	9	4.37	2.00–8.29	13.7				
35–44 years	46	1.87	1.36–2.48	9.5	3	1.11	0.23–3.25	0.1
45–54 years	103	1.31	1.07–1.59	7.3	9	1.10	0.50–2.08	0.2
≥55 years	119	0.88	0.72–1.05	−6.2	20	1.23	0.75–1.90	1.4

	Cardiovascular deaths			
	O	SMR	95% CI	AER*
Overall	269	1.04	0.92–1.17	1.2
Age at diagnosis				
<35 years				
35–44 years	21	2.04	1.26–3.12	3.9
45–54 years	60	1.17	0.89–1.51	2.6
≥55 years	188	0.95	0.82–1.10	−3.4

Risk of second non-hematological malignancies among 376,825 breast cancer survivors

Linda Morris Brown · Bingshu E. Chen · Ruth M. Pfeiffer · Catherine Schairer · Per Hall · Hans Storm · Eero Pukkala · Frøydis Langmark · Magnus Kaijser · Michael Andersson · Heikki Joensuu · Sophie D. Fosså · Lois B. Travis



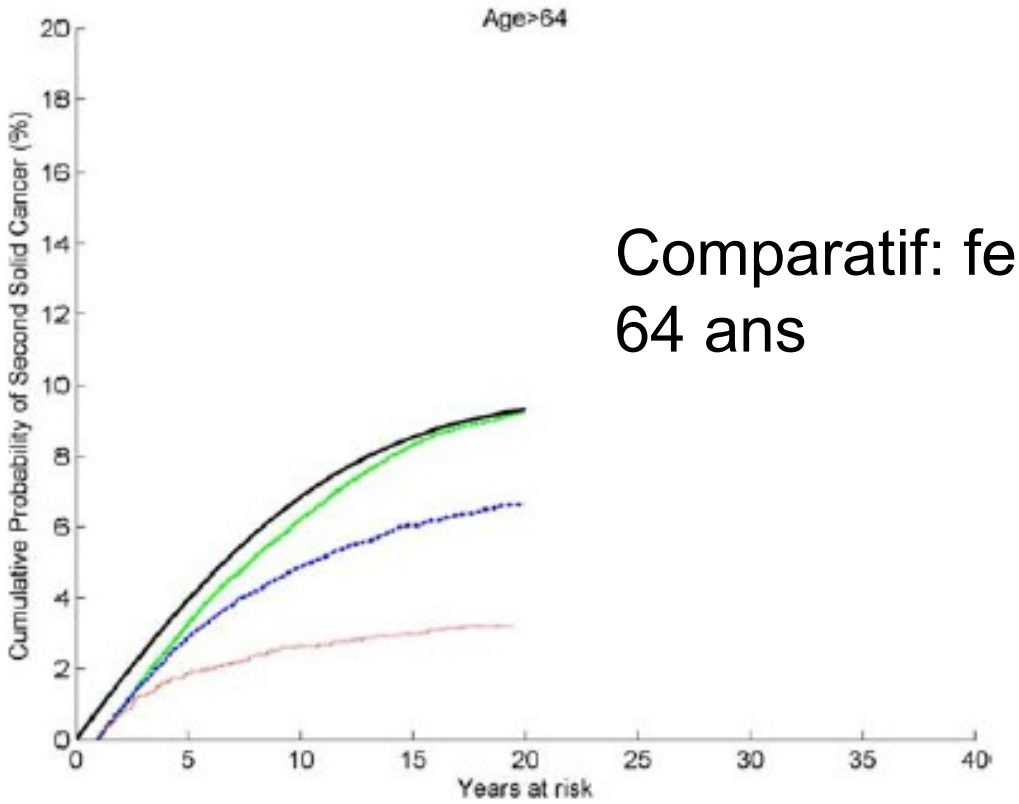
No. at risk									
Local	6833	4729	3505	2583	1646	1068	667	342	0
Regional	4577	1953	1209	756	455	272	179	105	0
Distant	343	73	37	20	11	9	7	3	0

Femmes de – de 40 ans au diagnostic, cancer localisé

Excès de risque de seconds cancers non hémato

Risk of second non-hematological malignancies among 376,825 breast cancer survivors

Linda Morris Brown · Bingshu E. Chen · Ruth M. Pfeiffer · Catherine Schairer · Per Hall · Hans Storm · Eero Pukkala · Frøydis Langmark · Magnus Kaijser · Michael Andersson · Heikki Joensuu · Sophie D. Fosså · Lois B. Travis



No. at risk									
Local	41062	20133	9290	3656	1022	0	0	0	0
Regional	22108	7373	2695	940	255	0	0	0	0
Distant	3423	519	129	47	13	0	0	0	0

Comparatif: femmes de + de 64 ans

Leukemia following breast cancer: an international population-based study of 376,825 women

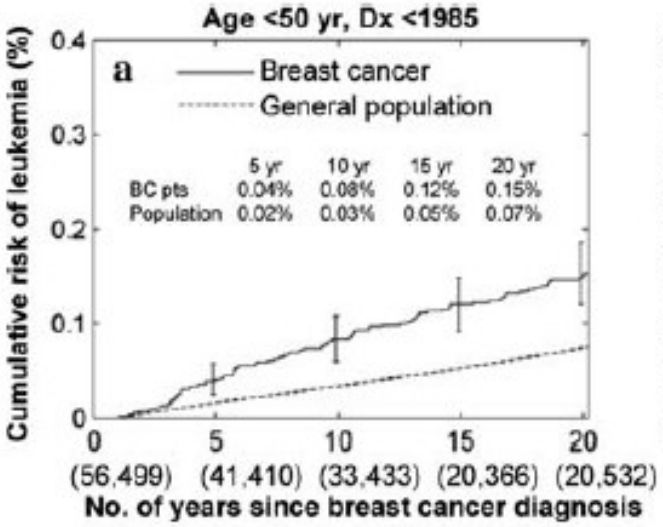
Regan A. Howard · Ethel S. Gilbert · Bingshu E. Chen · Per Hall · Hans Storm · Eero Pukkala · Froydis Langmark · Magnus Kaij · Michael Andersson · Heikki Joensuu · Sophie D. Fossa · Lois B. Travis

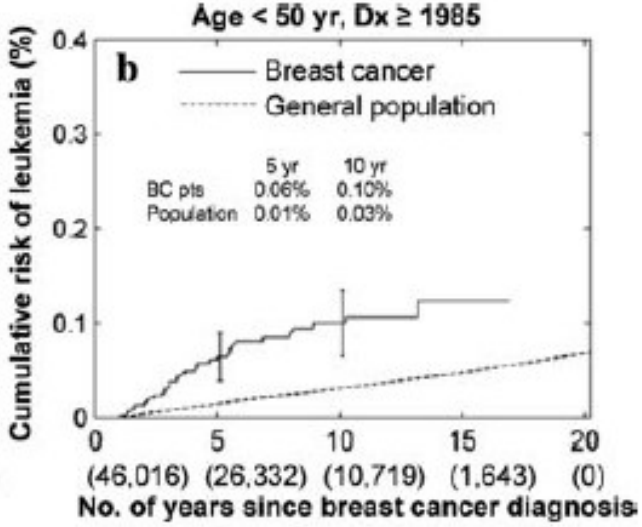
Breast Cancer Res Treat (2007) 105:359–368

Table 2 Excess absolute risk (EAR) of leukemia according to time since breast cancer diagnosis, age at breast cancer diagnosis,

Age at breast cancer diagnosis		
<40 years	32	9.03 (4.9–14.3)
40–49 years	119	7.22 (4.8–10.0)
50–59 years	171	10.49 (7.4–13.9)
60–69 years	204	12.10 (8.2–16.4)
≥70 years	161	6.12 (1.7–11.0)
		$P = 0.431$

Pas d'effet de l'âge





Cancer du sein controlatéral: Sur risque majeur chez les femmes les plus jeunes

VOLUME 26 · NUMBER 34 · DECEMBER 1 2008

JOURNAL OF CLINICAL ONCOLOGY

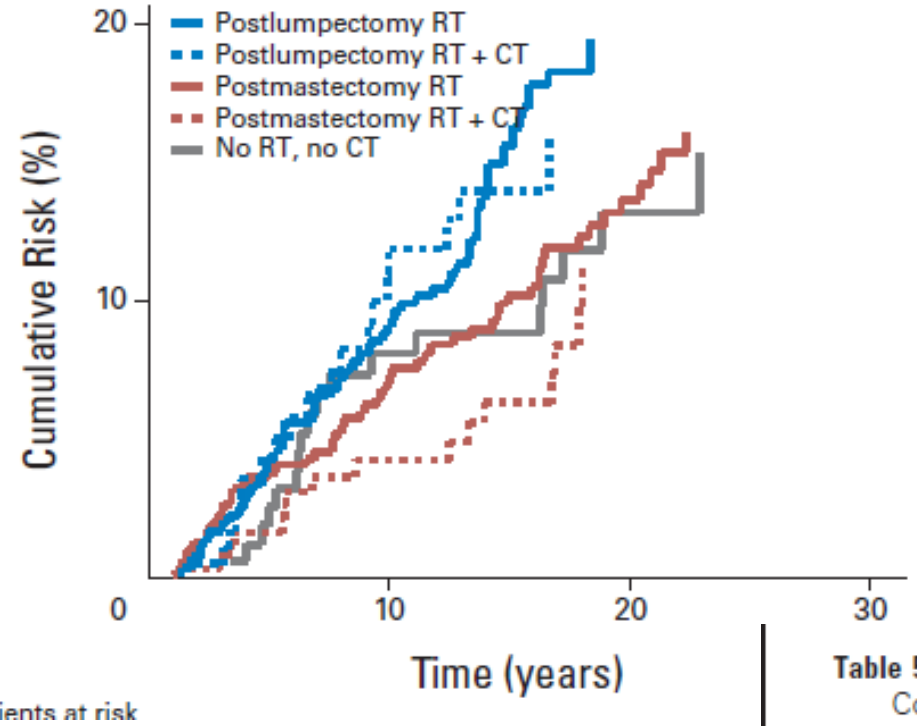
Roles of Radiotherapy and Chemotherapy in the Development of Contralateral Breast Cancer

Maartje J. Hooning, Berthe M.P. Aleman, Michael Hauptmann, Margreet H.A. Baaijens, Jan G.M. Klijn, Ruth Noyon, Marilyn Stovall, and Flora E. van Leeuwen

Table 2. Risk of Contralateral Breast Cancer by Follow-Up Interval, Age at Start of Treatment, and A

Characteristic	CBC			
	O	E	SIR	
Overall	503	173.0	2.91	
Follow-up interval, years				
1-4	157	40.9	3.84	
5-9	155	45.4	3.41	
10-14	104	43.6	2.39	
15-19	60	28.9	2.08	
≥ 20	27	14.3	1.89	
P_{trend}				< .001
Age at start of treatment, years				
< 35	40	4.7	8.46	
35-39	65	12.5	5.18	
40-44	82	24.7	3.32	
45-54	186	68.4	2.72	
≥ 55	130	62.5	2.08	
P_{trend}				< .001

Mais les traitements systémiques sont protecteurs



patients at risk

Rôle de la radiothérapie:
dose au sein controlatéral++

Table 5. Effect of Radiation Dose on Risk of Any CBC: Multivariate Cox Regression Analysis in Patients Treated at the NKI at Age < 45 Years (n = 1,044)

Average Radiation Dose to Contralateral Breast (Gy)	Risk of Any CBC*	
	HR	95% CI
0	1.0	Reference
0-2.2	0.95	0.49 to 1.84
2.2-4.1	1.67	0.85 to 3.27
≥ 4.1	2.15	1.04 to 4.43
Linear ERR per Gy†	0.21‡	0.01 to 0.61

Cancer du sein controlatéral:
Les traitements systémiques sont protecteurs

Table 6. Effect of Chemotherapy on Risk of CBC: Multivariate Cox Regression Analysis i

	Patients < 45 at BC Diagnosis			
	Strict Definition†		Broader Definition‡	
CT Versus No CT	HR	95% CI	HR	95% CI
Overall	0.76	0.53 to 1.10	0.69	0.50 to 0.95
Time-dependent model				
First 5 years of follow-up	0.66	0.35 to 1.28	0.48	0.28 to 0.82
Follow-up of 5 years and more	0.87	0.56 to 1.35	0.89	0.60 to 1.34

Risque de suicide après cancer du sein: excès modéré à long terme, pas d'effet de l'âge jeune

Table 1. Standardized mortality ratios (SMRs) and excess absolute risks (EARs) per 100 000 person-years for suicide among 723 810 1-year survivors of breast cancer

Characteristic	No. of breast cancer patients	Person-years of follow-up*	No. of suicides	SMR (95% CI)	EAR, No. of suicides per 100 000 person-years
All patients	723 810	5 598 156	836	1.37 (1.28 to 1.47)	4.1
Population-based cancer registry					
US SEER Program (1973–2001)	375 797	2 683 776	245	1.49 (1.32 to 1.70)	3.0
Sweden (1958–2001)	153 902	1 334 719	241	1.27 (1.12 to 1.45)	3.9
Denmark (1971–1999)	68 045	532 313	166	1.25 (1.07 to 1.46)	6.3
Finland (1953–2001)	71 099	570 780	125	1.53 (1.28 to 1.83)	7.6
Norway (1961–2000)	54 967	476 569	59	1.40 (1.07 to 1.81)	3.6
P for heterogeneity				.19	
Age at breast cancer diagnosis, y					
<40	46 275	432 278	63	1.34 (1.04 to 1.73)	3.8
40–49	132 397	1 275 941	226	1.42 (1.24 to 1.62)	5.3
50–59	163 790	1 400 210	244	1.50 (1.32 to 1.71)	5.8
60–69	170 211	1 344 622	176	1.26 (1.09 to 1.47)	2.8
≥70	211 137	1 145 104	127	1.24 (1.04 to 1.48)	2.2
P for heterogeneity				.30	

Pas d'effet âge

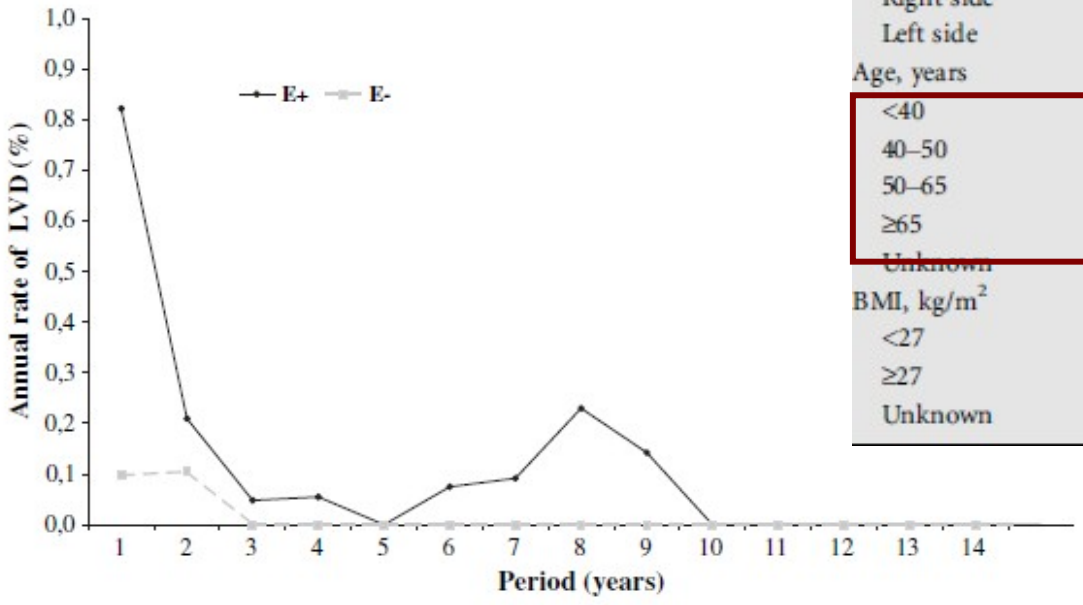
Risques cardiaques: anthracyclines

Long-term cardiac toxicity after adjuvant epirubicin-based chemotherapy in early breast cancer: French Adjuvant Study Group Results

P. Fumoleau[1]*, H. Roché[2], P. Kerbrat[3], J. Bonneterre, [illegible], A. Monnier[7], P. Montcuquet[8], M.-J. Goudier[9] & E. Luporsi[10]
On behalf of the French Adjuvant Study Group

Annals of Oncology 17: 85–92, 2006

Age jeune: risque moindre



Exposed E+	2,553	2,384	2,072	1,826	1,613	1,339	1,089	869	701	538	379	248	136	75
Exposed E-	1,024	952	837	762	669	589	490	379	289	198	134	81	44	23

Risk factor	No. of patients	LVD, *n* (%)	*P*
E cumulative dose (mg/m^2)			
0	1024	2 (0.2)	
<300	1040	11 (1.1)	0.59
300–600	1155	18 (1.6)	
≥600	279	4 (1.4)	
Unknown	79	0	
E dose intensity (mg/m^2/week)			
0	1024	2 (0.2)	
<20	1829	22 (1.2)	0.49
20–30	360	7 (1.9)	
≥30	237	4 (1.7)	
Unknown	127	0	
Radiotherapy			
No	158	0	
Right side	1,639	16 (1)	0.79
Left side	1,780	19 (1.1)	
Age, years			
<40	436	3 (0.7)	0.01
40–50	1,095	8 (0.7)	
50–65	1,589	13 (0.8)	
≥65	450	11 (2.4)	
Unknown	7	0	
BMI, kg/m^2			
<27	2294	20 (0.9)	0.03
≥27	779	14 (1.8)	
Unknown	504	1 (0.2)	

Risques cardiaques: trastuzumab

Incidence and Relative Risk (RR) of asymptomatic LVEF decrease with trastuzumab among patients.

Categories	No. of Studies	Trastuzumab	Control	Incidence (95% CI), % total	RR (95% CI)
Overall	8	456/5946	161/4513	7.5 (4.2–13.1)	2.13 (1.31–3.49)
Anthracyclines	6	441/5797	155/4377	7.2 (3.8–13.3)	2.13 (1.23–3.69)
Non-anthracycline	2	15/149	6/136	5.2 (0.2–56.6)	2.21 (0.90–5.41)
Sequential	5	434/5774	150/4538	7.5 (6.9–8.2)	2.35 (1.27–4.37)
Concurrent	1	7/23	5/19	30.4 (15.3–51.5)	1.16 (0.44–3.06)
Early stage	6	441/5797	155/4377	7.2 (3.8–13.3)	2.13 (1.23–3.69)
Metastatic disease	2	15/149	6/136	5.2 (0.2–56.6)	2.21 (0.90–5.41)

Table 3. Potential risk factors for the development of trastuzumab-associated cardiac dysfunction [21, 48, 49]

Cardiovascular factors	Noncardiovascular factors
Left ventricular dysfunction	Doxorubicin exposure
Coronary artery disease	Older age
Uncontrolled hypertension	Chest wall irradiation (especially to the left side)
Valvular heart disease	Diabetes
Cardiac arrhythmia	Obesity

Chen et al 2010, Martin et al 2009

Risques vitaux

- Y a-t-il un sur-risque de mortalité hors cancer du sein?
  - Oui, chez les femmes jeunes essentiellement par secondes tumeurs surtout liées à la raidothérapie et au contexte génétique (?)
  - le cancer du sein homo ou controlatéral étant de loin la cause N°1 de DC, pour lequel trts systémiques = protection
- Y a-t-il un sur-risque de pathologies liées aux trts systémiques menaçant le pronostic vital?
  - Oui, mais modéré chez les femmes jeunes
  - Hémopathies secondaires mais en diminution dans les dernières années
  - Risques cardiovasculaires, plus faibles que chez les femmes plus âgées

Deux types de risques à long terme

- Risques vitaux
- Altérations à long terme de la qualité de vie

Breast Cancer Res Treat (2010) 121:519–526
DOI 10.1007/s10549-009-0552-5

BRIEF REPORT

Health states of women after conservative surgery and radiation for breast cancer

Gary M. Freedman · Tianyu Li · Penny R. Anderson · Nicos Nicolaou · Andre Konski

Globalement, les femmes de – de 45 ans vont bien à long terme (ici, sans chimiothérapie)….

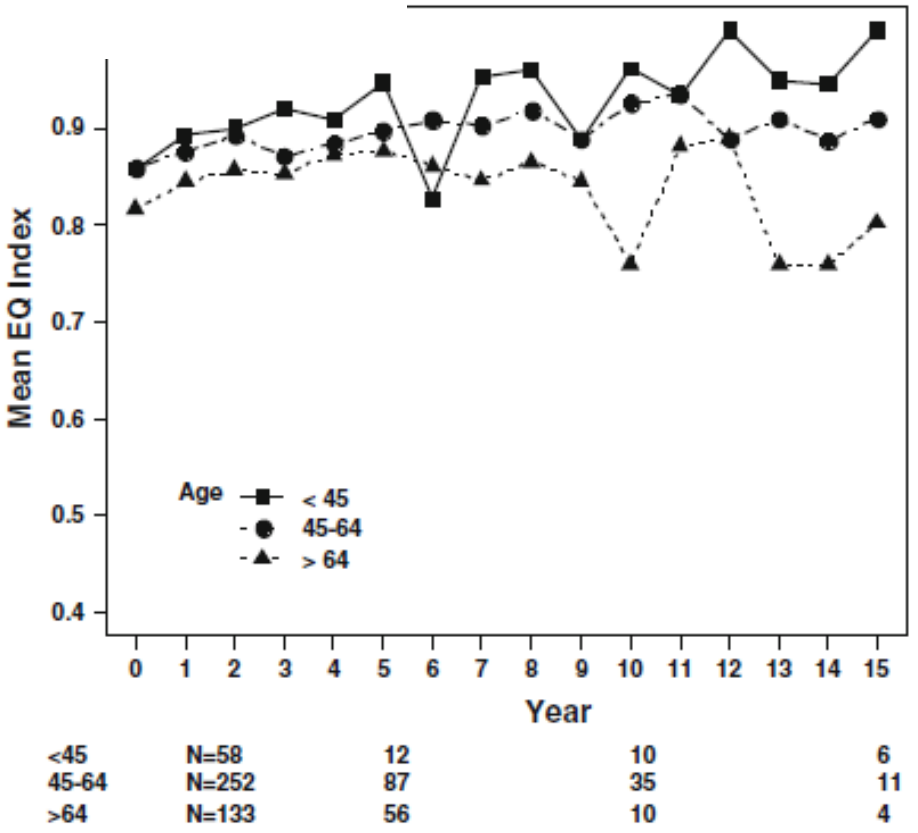


Fig. 2 Mean descriptive index scores by age for patients with breast cancer. The vertical axis is shortened and does not extend from 0 to 1, to improve readability of the figure

Résumé à long terme

- Qualité de vie, fatigue, fonctionnement physique et mental global:
  - Résultats altérés les premières années puis identiques globalement à la population générale
  - Association de mauvais résultats à dépression, douleur, symptômes ménopausiques, faibles revenus, mais pas à l'âge
  - Association avec traitements systémiques ++ dont chimio +++
  - Chez les femmes jeunes association forte avec symptômes gynéco-ménopausiques

A long terme, les femmes de – de 45 ans au diagnostic sont très médicalisées

L. V. van de Poll-Franse
F. Mols
A. J. J. M. Vingerhoets
A. C. Voogd
R. M. H. Roumen
J. W. W. Coebergh

Increased health care utilisation among 10-year breast cancer survivors

Support Care Cancer (2006) 14: 436–443

Table 4 Univariate association between patient- and tumour characteristics at diagnosis, questionnaire outcome and health care utilisation during the past 12 months (before the study)

	Visited during past 12 months				
	General practitioner	Specialist	Physical therapist	Complementary caregiver	Patient support group
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Patient and tumour characteristics					
Current age (years)					
45–54	1.0	1.0	1.0	1.0	1.0
55–64	0.8 (0.2–3.1)	0.7 (0.2–2.4)	0.7 (0.3–1.8)	0.3 (0.1–1.2)	1.1 (0.2–6.1)
65–74	0.8 (0.2–3.2)	0.8 (0.2–2.9)	0.4 (0.1–1.0)*	0.3 (0.1–1.2)	0.2 (0.1–2.3)
75+	1.2 (0.2–6.5)	0.8 (0.2–3.1)	0.4 (0.1–1.1)	0.3 (0.1–1.5)	1.3 (0.2–8.3)

Etude néerlandaise, cancers du sein en 1993, étude en 2005
Traitements systémiques: 26%!

Un problème émergent majeur: les alopécies résiduelles à long terme (partielles ou complètes)

Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer

C. Prevezas
B. Matard
L. Pinquier*
P. Reygagne

British Journal of Dermatology 2009 **160,** pp881–898

Incidence inconnue: 2-5%?

H Bourgeois et al: Etude Alopers OMIT Bretagne Pays de Loire (SABCS 09)

- 81 femmes et un homme souffrant de mauvaise repousse ou alopécie résiduelle de 1 à 6 ans après la fin de la chimio
- Age médian: 60 ans [35-78]

FEC 100 + docetaxel 100 +/- traztuzumab	67
FEC 100 + docetaxel 100 + paclitaxel	1
FEC 75 + docetaxel 75	1
6 FEC 100	2
6 docetaxel 100	4
Epirubicin 100 or 75 + TXT 75	2
Traztuzumab + docetaxel +/- carboplatine	5

Pistes…

Cardiotoxicité	Limiter les anthracyclines (fait) Améliorer RT (fait) Surveillance post-trastu +++
Hémopathies secondaires	Limiter les alkylants, limiter les anthracyclines (fait) Attention autres drogues interagissant avec réparation?
Qualité de vie	Médicalisation long terme, accompagnement post-thérapeutique++
Non repousse des cheveux	Attention au docetaxel: proposer casque pdt perfusion? (protocole H Bourgeois)