Malattie neurodegenerative e tumori: dall'epidemiologia alle ipotesi eziopatologiche

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La senescenza

- Perchè tutti gli individui hanno una caratteristica genetica la cui espressione fenotipica è la senescenza e la morte?

- Quali sono i determinanti di questo processo sfavorevole condiviso da tutti gli individui?

- Perchè i geni sfavorevoli che determinano questo processo negativo sono sfuggiti alla selezione naturale?

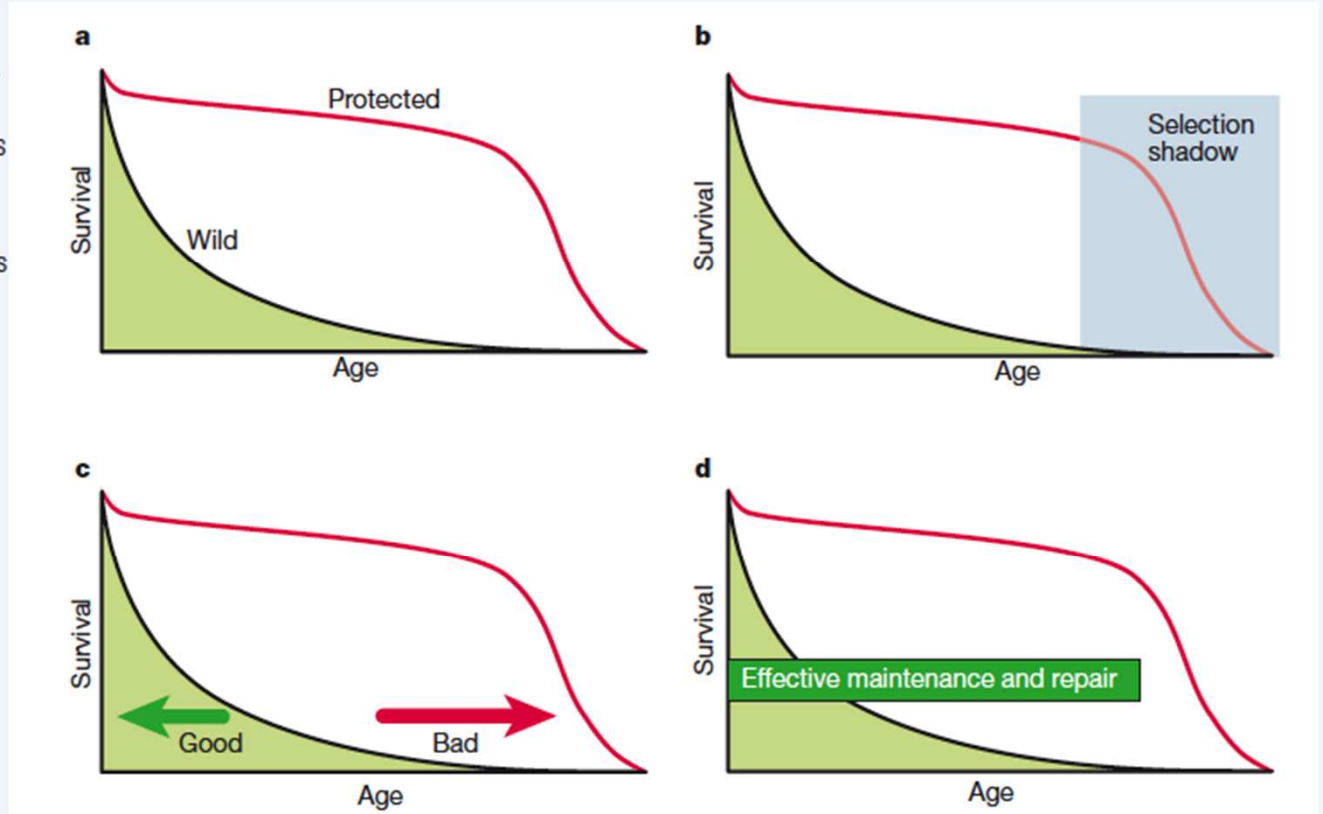
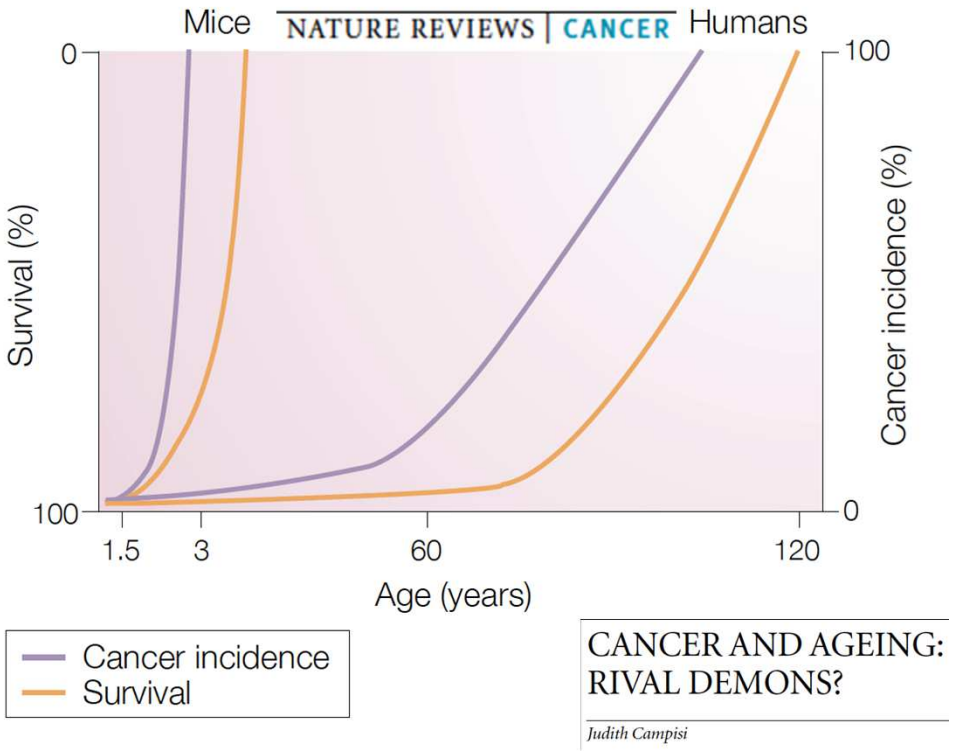


Figure 1 Evolutionary theories of ageing. **a**, Extrinsic mortality in wild environments occurs to an extent that senescence-associated mortality is rare, undermining any idea that genes specifically for ageing have evolved. **b**, The 'selection shadow' at older ages may permit an accumulation of late-acting deleterious mutations (mutation-accumulation theory). **c**, Pleiotropic genes that benefit organisms early in life will be favoured by selection even if they have bad effects at later ages (pleiotropy theory). **d**, Selection pressure to invest metabolic resources in somatic maintenance and repair is limited; all that is required is to keep the organism in sound condition for as long as it might survive in the wild (disposable-soma theory).

Due teorie principali basate sull'idea che la forza della selezione naturale diminuisca con il progredire dell'età possono spiegare il fenomeno della senescenza

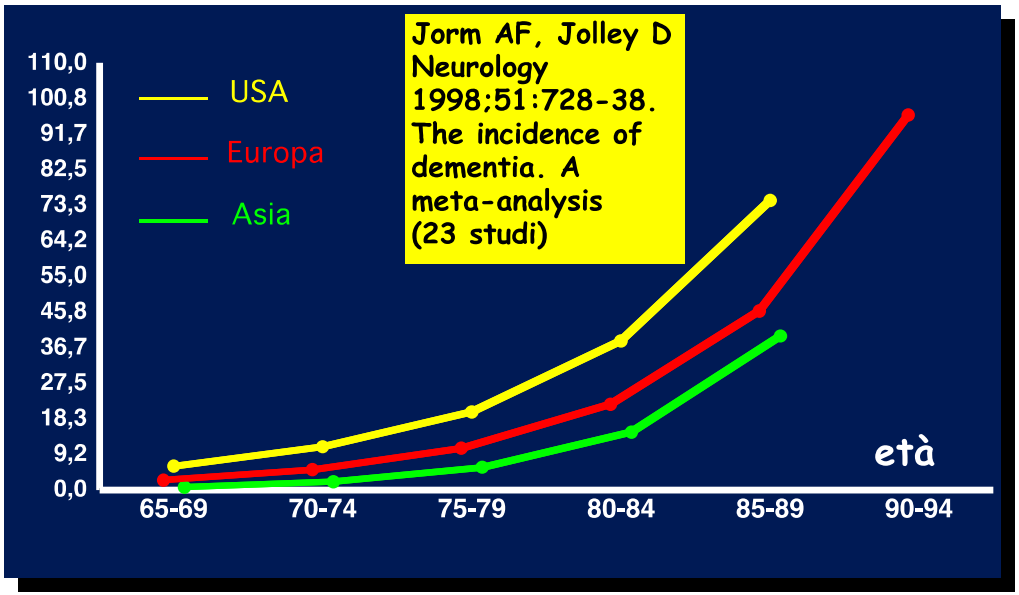
- **Accumulo delle mutazioni**
  - Gli alleli mutati dannosi che si esprimono nelle fasi iniziali della vita sono controllati dalla selezione naturale
  - Questi alleli, quando si esprimono tardi nel corso della vita sono meno controllati dalla selezione naturale e hanno la possibilità di essere trasmessi e accumularsi di generazione in generazione
    - Molte mutazioni
- **Pleiotropismo antagonista**
  - Geni pleiotropici con effetti favorevoli nella fase iniziale della vita e con effetti negativi di grandezza confrontabile in età anziana sono favoriti dalla selezione naturale
  - La selezione naturale spinge gli individui a possedere questi geni
    - Un numero limitato di mutazioni

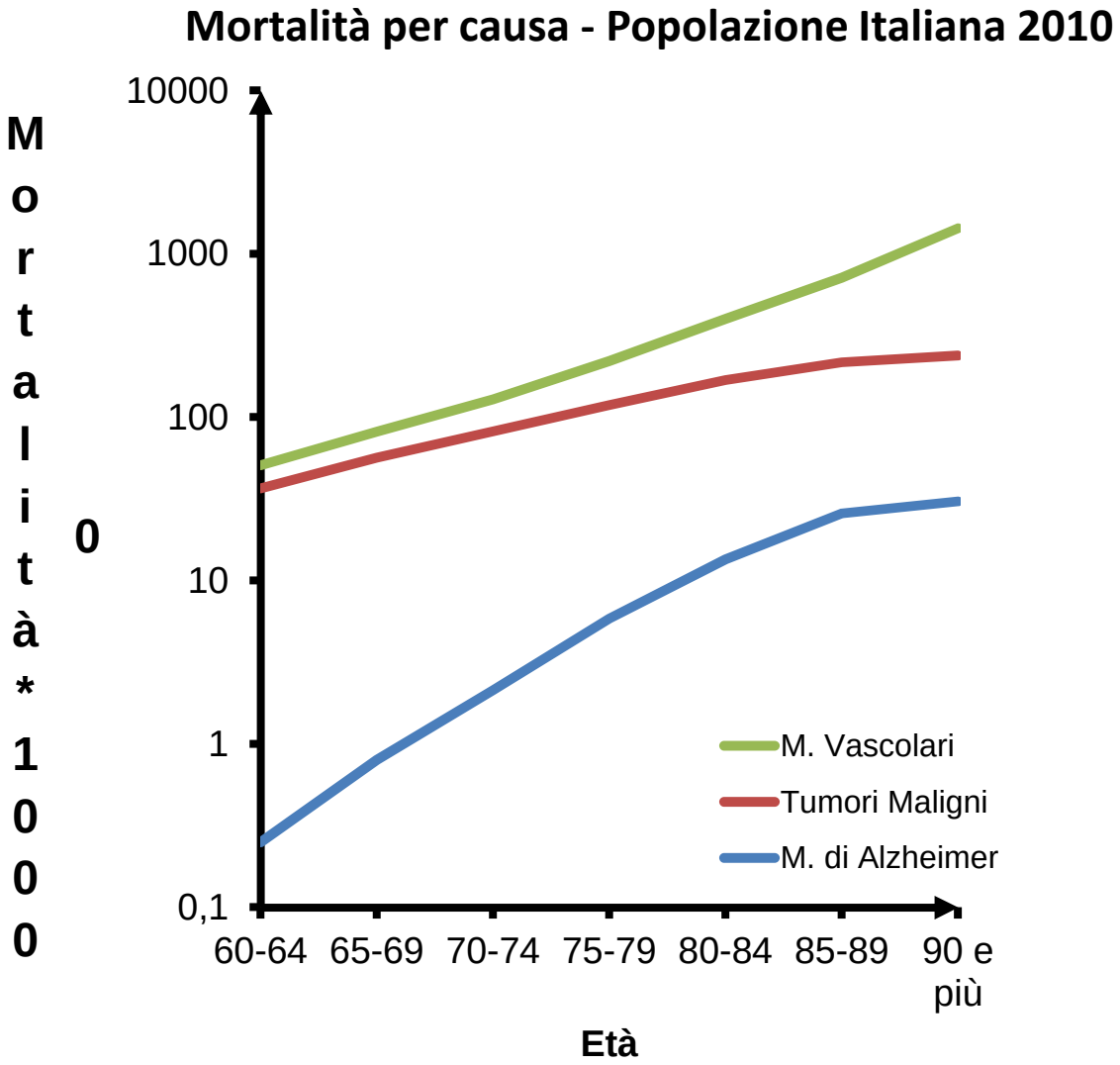
Cancro e neurodegenerazione sono manifestazioni della senescenza?



CANCER AND AGEING: RIVAL DEMONS?

Judith Campisi




Mortalità per causa - Popolazione Italiana 2010
Mortalità * 10000
10000
1000
100
10
1
0,1
0
60-64
65-69
70-74
75-79
80-84
85-89
90 e più
Età
M. Vascolari
Tumori Maligni
M. di Alzheimer

CANCER AND AGEING: RIVAL DEMONS?

Judith Campisi

Organisms with renewable tissues use a network of genetic pathways and cellular responses to prevent cancer. The main mammalian tumour-suppressor pathways evolved from ancient mechanisms that, in simple post-mitotic organisms, act predominantly to regulate embryogenesis or to protect the germline. The shift from developmental and/or germline maintenance in simple organisms to somatic maintenance in complex organisms might have evolved at a cost. Recent evidence indicates that some mammalian tumour-suppressor mechanisms contribute to ageing. How might this have happened, and what are its implications for our ability to control cancer and ageing?

Summary

- Cancer is a problem that affects organisms with renewable tissues; these have evolved tumour-suppressor mechanisms to suppress the development of cancer.
- Tumour-suppressor genes act to prevent or repair genomic damage (caretakers), or inhibit the propagation of potential cancer cells (gatekeepers) by permanently arresting their growth (cellular senescence) or inducing cell death (apoptosis).
- Some caretaker tumour suppressors seem to postpone the development of ageing phenotypes, and so are also longevity-assurance genes.
- The gatekeeper tumour-suppressor mechanisms (apoptosis and cellular senescence), by contrast, might promote certain ageing phenotypes.
- Apoptosis and cellular senescence are controlled by the p53 and RB tumour-suppressor pathways, components of which are evolutionarily conserved among multicellular organisms.
- The evolutionary hypothesis of antagonistic pleiotropy predicts that some processes that benefit young organisms (by suppressing cancer, for example) can have detrimental effects later in life and would therefore contribute to ageing.
- Both apoptosis and cellular senescence might be antagonistically pleiotropic, promoting ageing by exhausting progenitor or stem cells. Additionally, senescent cells secrete factors that can disrupt tissue integrity and function, and even promote the progression of late-life cancers.
- Recent studies on p53 provide a molecular basis for how tumour suppression and ageing might be intertwined.

Aging Cell (2012) **11,** pp378–383 Doi: 10.1111/j.1474-9726.2012.00807.x

REVIEW

Stefano Giaimo[1,2] and Fabrizio d'Adda di Fagagna[1,3]

Is cellular senescence an example of antagonistic pleiotropy?

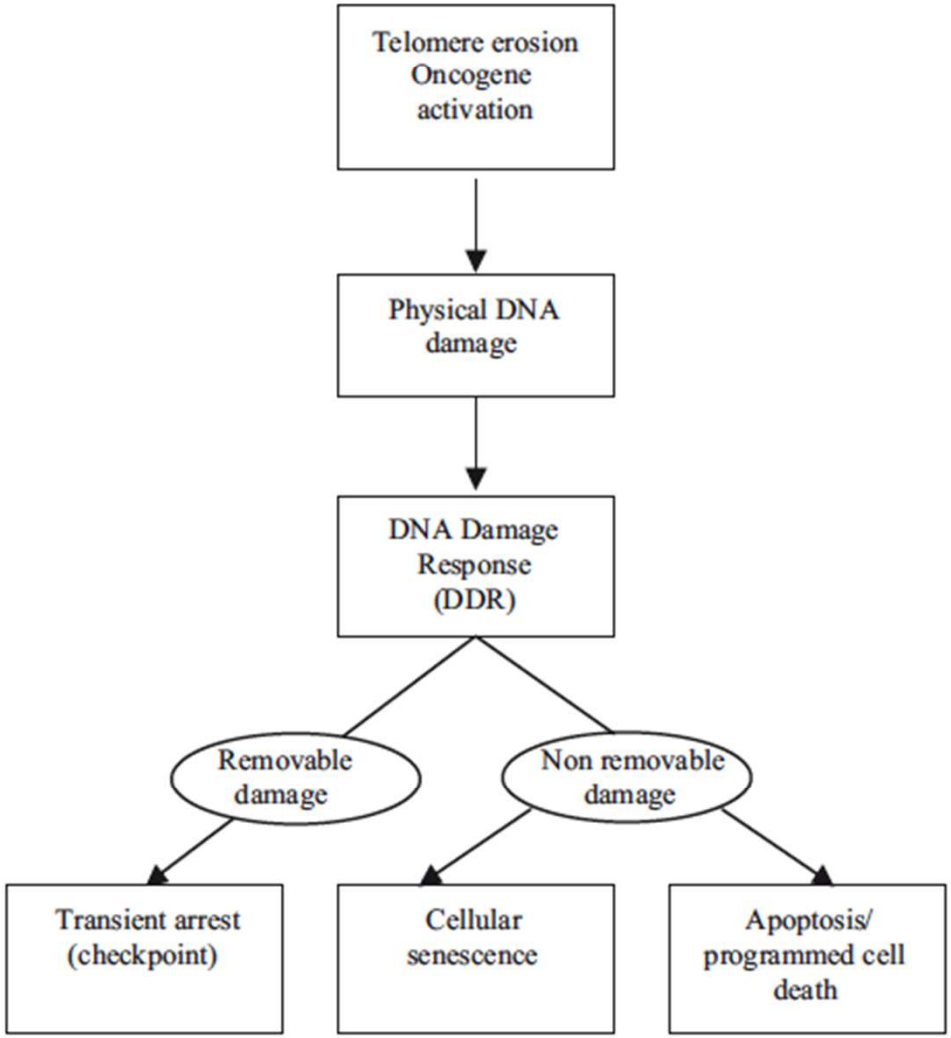


Fig. 1 Cellular senescence as a DNA damage response.

Do tumor-suppressive mechanisms contribute to organism aging by inducing stem cell senescence?

Pier Giuseppe Pelicci

J. Clin. Invest. **113**:4–7 (2004). doi:10.1172/JCI200420750.

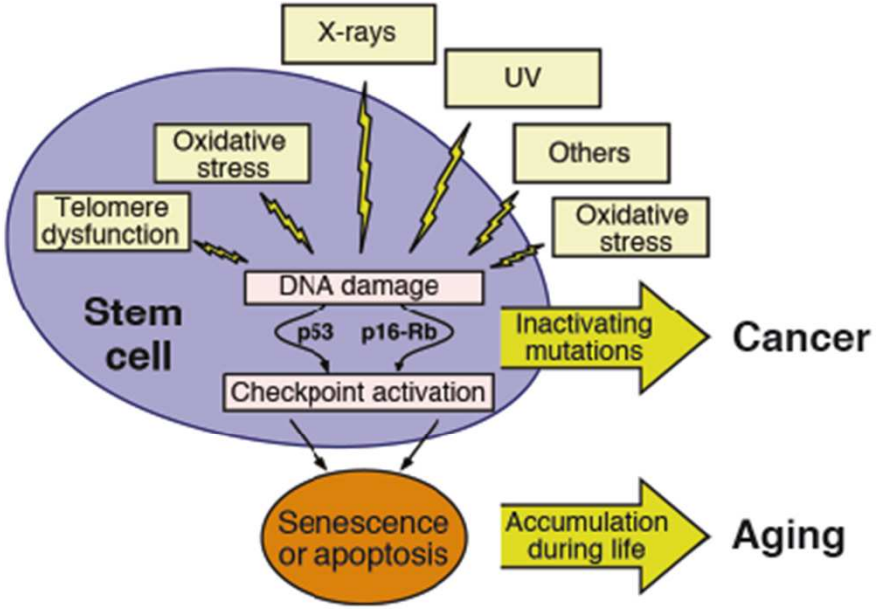


Figure 1

DNA damage accumulates as the consequence of endogenous (telomere dysfunction, oxidative stress) or exogenous (oxidative stress, γ-irradiation, UV light, and others) attacks. Damaged DNA activates checkpoint responses that are mediated by the p53 and p16-Rb pathways and that result in apoptosis or cellular senescence. If these events occur in stem/progenitor cells, tissue homeostasis is altered — a phenomenon that might contribute to aging. If, instead, DNA mutations that inactivate these checkpoint pathways accumulate, then cancer can arise.

Alzheimer disease and cancer

Abstract—Cross-sectional studies raise the possibility of protective relationships between, or a common mechanism underlying, the development of dementia of the Alzheimer type (DAT) and cancer. Using a prospective longitudinal design, the authors found that the risk of developing cancer is less among participants with DAT vs nondemented participants ($p < 0.001$) and that the risk of developing DAT may be less for participants with a history of cancer ($p = 0.060$).

NEUROLOGY 2005;64:895–898

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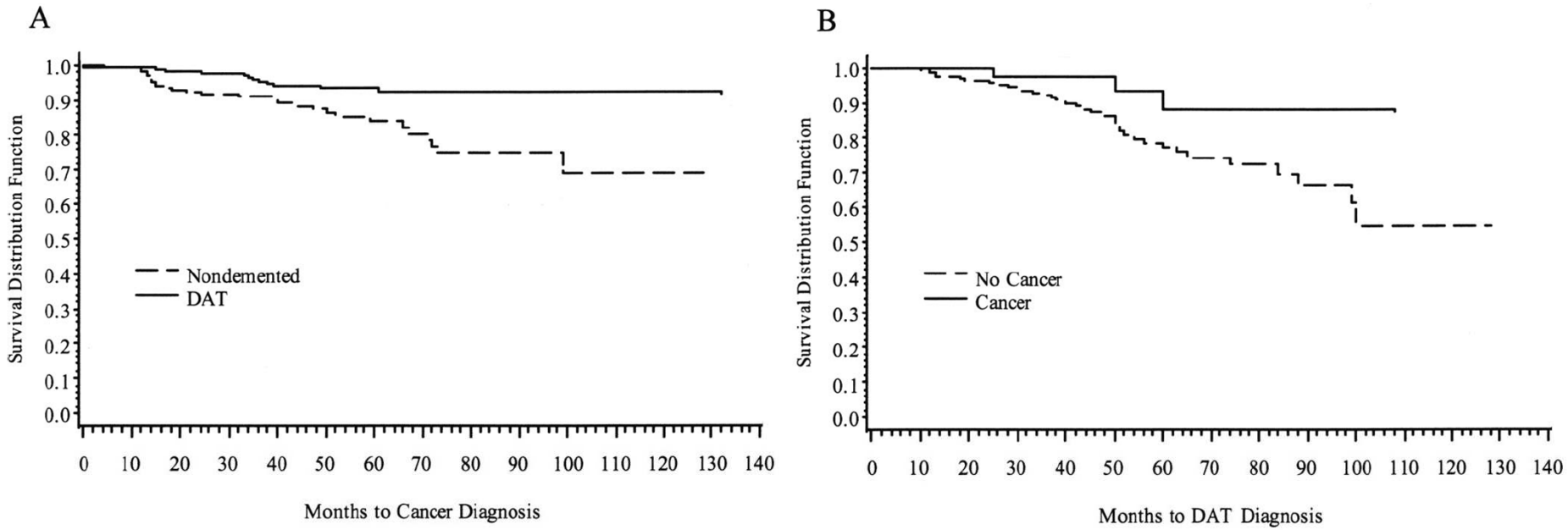

Figure. Kaplan–Meier survival curves for the study groups. (A) Time from first assessment to cancer diagnosis as a function of a diagnosis of dementia of the Alzheimer type (DAT) and no dementia at study entry ($p < 0.001$). *(B) Time from first assessment to DAT diagnosis as a function of a history of cancer at study entry* ($p = 0.060$).

ARTICLES

Cancer linked to Alzheimer disease but not vascular dementia

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ABSTRACT

Objective: To investigate whether cancer is associated with Alzheimer disease (AD) and vascular dementia (VaD).

Methods: Cox proportional hazards models were used to test associations between prevalent dementia and risk of future cancer hospitalization, and associations between prevalent cancer and risk of subsequent dementia. Participants in the Cardiovascular Health Study–Cognition Substudy, a prospective cohort study, aged 65 years or older (n = 3,020) were followed a mean of 5.4 years for dementia and 8.3 years for cancer.

Results: The presence of any AD (pure AD + mixed AD/VaD; hazard ratio [HR] = 0.41, 95% confidence interval [CI] = 0.20–0.84) and pure AD (HR = 0.31, 95% CI = 0.12–0.86) was associated with a reduced risk of future cancer hospitalization, adjusted for demographic factors, smoking, obesity, and physical activity. No significant associations were found between dementia at baseline and rate of cancer hospitalizations for participants with diagnoses of VaD. Prevalent cancer was associated with reduced risk of any AD (HR = 0.72; 95% CI = 0.52–0.997) and pure AD (HR = 0.57; 95% CI = 0.36–0.90) among white subjects after adjustment for demographics, number of *APOE* ϵ4 alleles, hypertension, diabetes, and coronary heart disease; the opposite association was found among minorities, but the sample size was too small to provide stable estimates. No significant association was found between cancer and subsequent development of VaD.

Conclusions: In white older adults, prevalent Alzheimer disease (AD) was longitudinally associated with a reduced risk of cancer, and a history of cancer was associated with a reduced risk of AD. Together with other work showing associations between cancer and Parkinson disease, these findings suggest the possibility that cancer is linked to neurodegeneration. ***Neurology*® 2010;74:106–112**

Table 3 Results of Cox proportional hazards models[a] testing time to first cancer hospitalization as it relates to having a particular dementia diagnosis vs no dementia at baseline

Predictor	Baseline status		HR	95% CI	*p*
	No dementia (n)	Dementia diagnosis (n)			
Pure AD	2,107	71	0.31	0.12–0.86	0.0237
Any AD (pure AD + mixed AD/VaD)	2,107	118	0.41	0.20–0.84	0.0145
Mixed AD/VaD	2,107	47	0.58	0.21–1.56	0.2765
Any VaD (pure VaD + mixed AD/VaD)	2,107	76	0.89	0.45–1.77	0.7441
Pure VaD	2,107	29	1.64	0.66–4.11	0.2885
Any dementia diagnosis	2,107	165	0.70	0.42–1.17	0.1730

Abbreviations: AD = Alzheimer disease; CI = confidence interval; HR = hazard ratio; VaD = vascular dementia.

[a]Adjusted for the Cardiovascular Health Study clinic effect, sex, race, education, age, income, smoking, >130% overweight, and kilocalories expended in physical activity.

Inverse association between cancer and Alzheimer's disease: results from the Framingham Heart Study

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Table 3| **Association between history of cancer at examination 20 (baseline) and incident dementia in Framingham Heart Study, after adjustment**

	No of cancers		Hazard ratio (95% CI)*		
				Alzheimer's disease	
Model and cancer types	At baseline	Incident cases	Any dementia	Possible	Probable
Model 1 (n=1274)†:			n=322	n=256	n=220
All‡	175	247	0.83 (0.63 to 1.10)	0.81 (0.59 to 1.11)	0.67 (0.47 to 0.97)
Smoking related§	54	96	0.79 (0.45 to 1.39)	0.62 (0.31 to 1.26)	0.26 (0.08 to 0.82)
Non-smoking related	127	177	0.84 (0.62 to 1.13)	0.87 (0.62 to 1.21)	0.82 (0.57 to 1.19)
Model 2 (n=1037)¶:			n=263	n=212	n=185
All‡	133	210	0.92 (0.68 to 1.26)	0.90 (0.64 to 1.28)	0.76 (0.52 to 1.12)
Smoking related§	40	77	0.66 (0.32 to 1.33)	0.62 (0.28 to 1.41)	0.34 (0.11 to 1.08)
Non-smoking related	97	157	0.99 (0.72 to 1.38)	0.99 (0.68 to 1.42)	0.91 (0.61 to 1.35)

*Calculated using Cox proportional hazards modelling.

†Adjusted for age, sex, smoking, and incident cancer.

‡Does not include non-melanoma skin cancers.

§Defined as cancer of the oral cavity, pharynx, larynx, oesophagus, stomach, pancreas, lung, cervix, bladder, and kidney.

¶Additionally adjusted for apolipoprotein E4 status, education, and homocysteine level.

BMJ 2012;344:e1442 doi: 10.1136/bmj.e1442 (Published 12 March 2012)

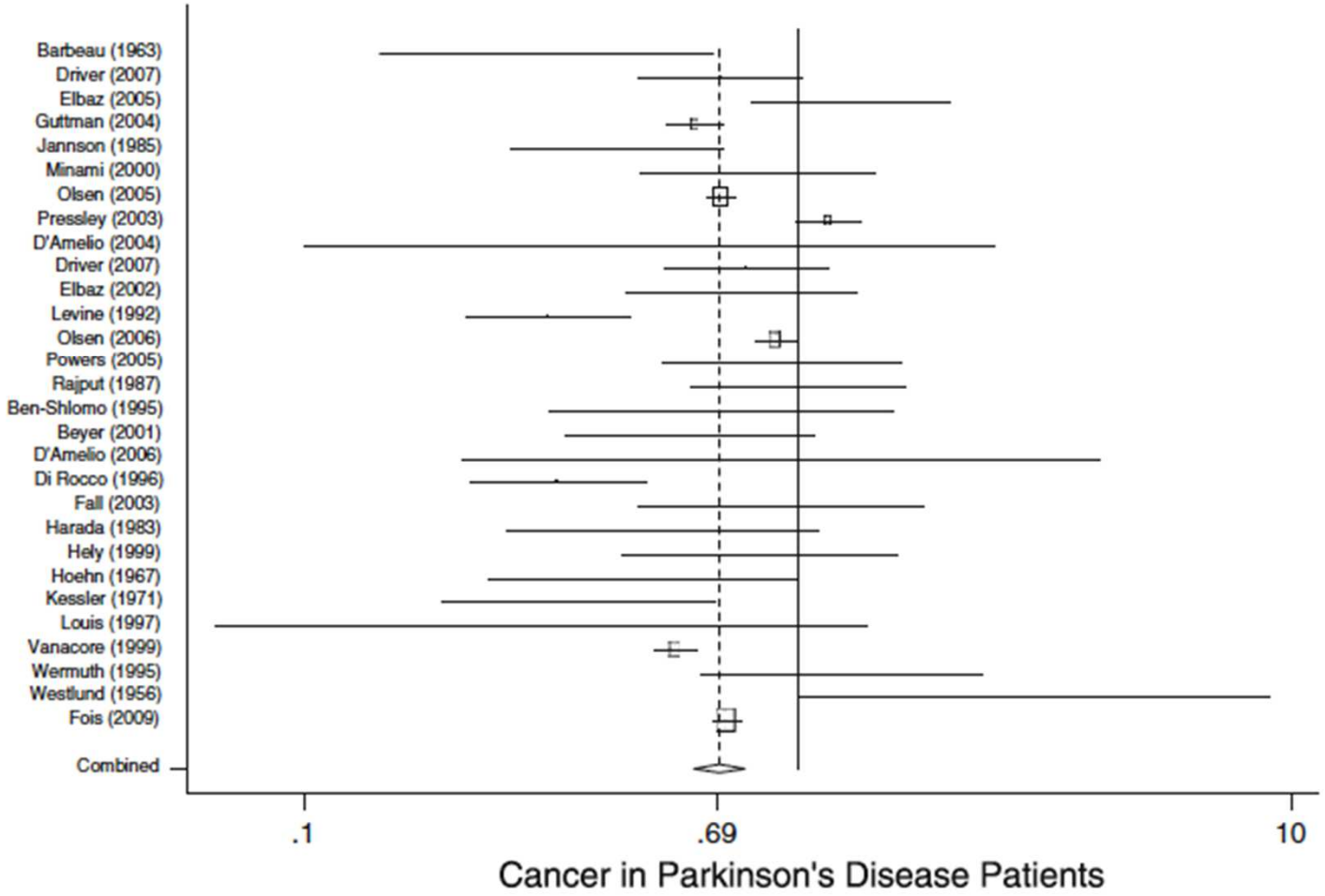


Fig. 2 Relative risks of cancer in patients with PD, excluding melanoma and other skin cancers where possible, in 29 studies. The graph shows the estimates and confidence intervals for each study, together with a combined estimate (*dotted vertical line*) and confidence interval (*diamond-shaped box*) from the random-effects model. The estimates are plotted with *boxes*; the area of each box is inversely proportional to the estimated effect's variance in the study, hence giving more visual prominence to studies where the effect is more precisely estimated

Table 2. Estimated RRs for Melanoma and PD

Relationship	Observed, No.	Expected, No.	RR (95% CI)
Estimates of RR for Melanoma Among 2998 Individuals With PD Who Died (Self) and Their Relatives			
Self	48	24.6	1.95 (1.44-2.59)
First-degree relative	217	176.8	1.23 (1.07-1.40)
Second-degree relative	429	383.1	1.12 (1.02-1.23)
Third-degree relative	1013	958.4	1.06 (0.99-1.12)
Estimates of RR for PD Death Among 7841 Individuals With Melanoma (Self) and Their Relatives			
Self	48	29.1	1.65 (1.22-2.19)
First-degree relative	203	157.9	1.29 (1.12-1.48)
Second-degree relative	391	331.4	1.18 (1.07-1.30)
Third-degree relative	856	765.6	1.12 (1.04-1.20)

Abbreviations: PD, Parkinson disease; RR, relative risk.

Table 3. Estimated RRs for Prostate Cancer and PD

Relationship	Observed, No.	Expected, No.	RR (95% CI)
Estimates of RR for Prostate Cancer Among the 2998 Individuals With PD Who Died (Self) and Their Relatives			
Self	212	124.1	1.71 (1.49-1.96)
First-degree relative	765	613.6	1.25 (1.16-1.34)
Second-degree relative	1194	1098.7	1.09 (1.03-1.15)
Third-degree relative	3504	3251.1	1.08 (1.04-1.11)
Estimates of RR for Death With PD Among the 22 147 Individuals With Prostate Cancer (Self) and Their Relatives			
Self	212	152.4	1.39 (1.21-1.59)
First-degree relative	656	531.8	1.23 (1.14-1.33)
Second-degree relative	845	781.6	1.08 (1.01-1.16)
Third-degree relative	1703	1550.5	1.10 (1.05-1.15)

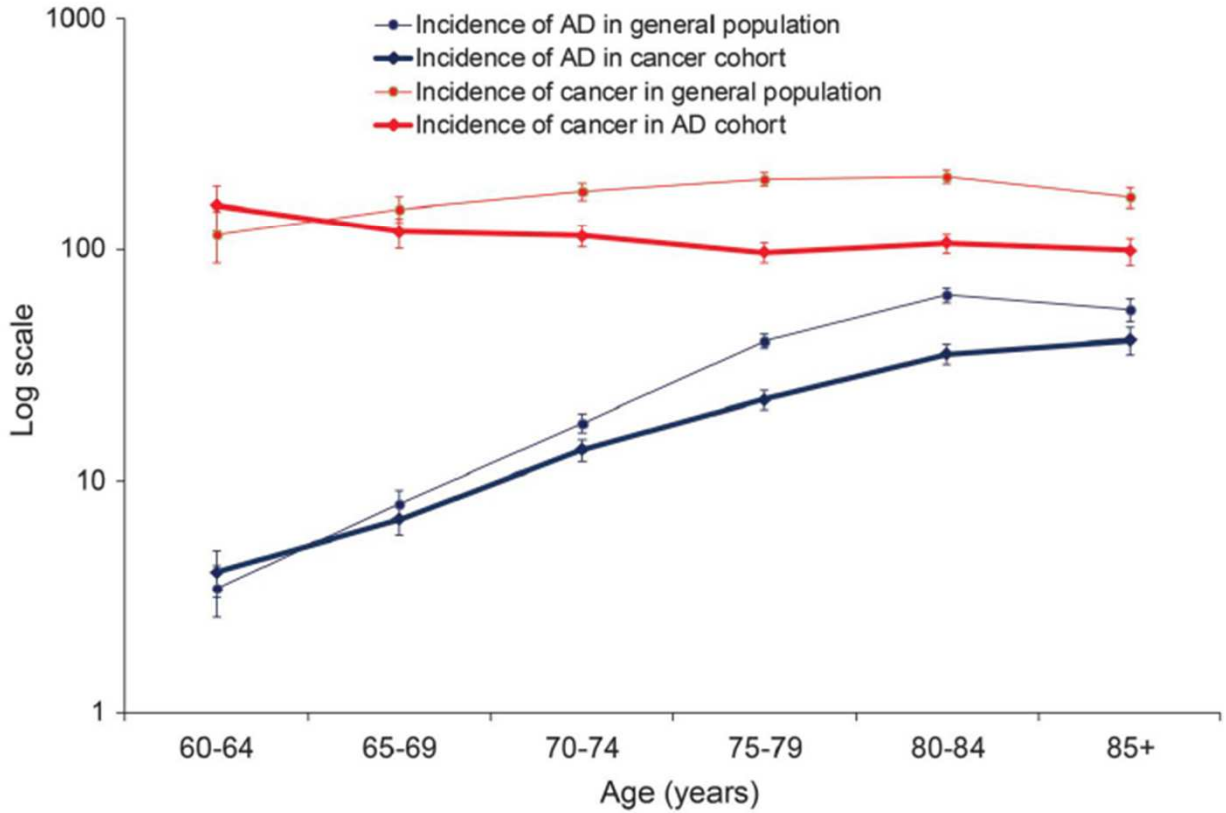
Abbreviations: PD, Parkinson disease; RR, relative risk.

Table 2 Observed and expected cases and relative risk of occurrence of Alzheimer disease dementia in the cohort of persons with cancer and of cancers in the cohort of persons with AD dementia[a]

	Cancers in AD dementia cohort		AD dementia in cancer cohort	
	Obs/exp[b]	RR (95% CI)	Obs/exp[b]	RR (95% CI)
Total	161/281.2	0.57 (0.49-0.67)	161/246.0	0.65 (0.56-0.76)
Before the diagnosis	68/163.4	0.42 (0.32-0.53)	93/140.1	0.66 (0.54-0.81)
After the diagnosis	93/117.8	0.79 (0.64-0.97)	68/105.9	0.64 (0.50-0.81)
In survivors	78/184.4	0.42 (0.33-0.53)	78/135.1	0.58 (0.46-0.72)
In nonsurvivors	83/96.8	0.86 (0.68-1.06)	83/110.9	0.75 (0.60-0.93)
Cancer type				
Epithelial	132/219.9	0.60 (0.50-0.71)	132/200.2	0.66 (0.55-0.78)
Mesenchymal	3/5.2	0.58 (0.12-1.70)	3/4.4	0.69 (0.14-2.00)
Blood	9/19.1	0.47 (0.21-0.89)	9/16.3	0.55 (0.25-1.05)
Nervous system	3/4.3	0.70 (0.14-2.05)	3/2.6	1.17 (0.23-3.41)
Unspecified	14/32.8	0.43 (0.23-0.72)	14/22.5	0.62 (0.34-1.04)
Cancer site				
Breast	26/37.0	0.70 (0.46-1.03)	26/38.1	0.68 (0.45-1.00)
Lung	16/26.6	0.60 (0.34-0.98)	16/18.7	0.85 (0.49-1.39)
Bladder	18/22.4	0.81 (0.48-1.27)	18/22.9	0.79 (0.47-1.24)
Prostate	19/20.3	0.94 (0.56-1.46)	19/22.0	0.87 (0.52-1.35)
Colorectal	13/30.0	0.43 (0.23-0.74)	13/29.5	0.44 (0.23-0.75)
Other	69/145.0	0.48 (0.37-0.60)	69/114.8	0.60 (0.47-0.76)

Abbreviations: AD = Alzheimer disease; CI = confidence interval; RR = relative risk.
[a] Expectations are calculated with reference to the general population of the same sex, age, and calendar year of follow-up.
[b] Observed vs expected values.

Figure 1 **Age-specific incidence rates of cancers and Alzheimer disease dementia**



Age-specific incidence rates of cancers in the general population and in the cohort of persons with Alzheimer disease (AD) dementia, and age-specific incidence rates of AD dementia in the general population and in the cohort of persons with cancers, ×10,000 person-years.

AD dementia and cancer can be viewed as opposite faces of senescence, and interpreting these diseases within the unitary context of senescence processes, particularly if our results are confirmed in future epidemiologic and laboratory studies, might represent a valuable opportunity for knowledge and human health.