con il patrocinio di

Associazione Italiana di Epidemiologia

Dipartimento Attività Integrate Ricerca e Innovazione AOU AL - ASL AL

CPO

Epidemiologia occupazionale e amianto:
ricerca, salute, giustizia e dialogo con la comunità

L'eredità di Dario Mirabelli

27 APRILE 2026

AULA MAGNA DENTAL SCHOOL
Città della Salute e della Scienza di Torino
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Anticipazione della malattia neoplastica: quando il buon senso è fuorviante

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Sistema Socio Sanitario Regione Lombardia

Anticipazione di malattia

Idea

- Esposizioni più “elevate” (intensità, durata) fanno venire prima una malattia (a minori età e latenza)?

Dove se ne parla

- **Ambito medico-legale**: domanda tipica nei processi: “L’esposizione ad amianto ha anticipato il decesso per mesotelioma?”
- **Comunicazione del rischio:** anticipazione più comprensibile del rischio relativo per i non tecnici

Possibili risposte

- **Buon senso**: calcolo **età/latenza** alla diagnosi nei malati; **correlazione** tra durata esposizione e latenza nei malati
- **Approccio corretto**: principi epidemiologici e statistici

1. Età alla diagnosi/decesso

Libri e articoli che sconsigliano il calcolo dell'età alla diagnosi

- Hill AB. Principles of medical statistics. Eight Edition. XXII: Further fallacies and difficulties. Lancet The Lancet Limited 1967:296-298.
- Pike MC, Doll R. Age at onset of lung cancer: significance in relation to effect of smoking. Lancet 1965:1(7387):665-668.
- Colton T. Fallacies in numerical reasoning, in Statistics in Medicine. Boston: Little, Brown and Company 1974:297-299
- Rothman KJ Epidemiology. An Introduction. 1st, 2nd, 3rd Edition. New York: Oxford University Press; 2002, 2012, 2014.
- Weiss NS. Exercises in Epidemiology. Applying Principles and Methods., New York: Oxford University Press 2012.
- Hanley JA, Foster BJ. Avoiding blunders involving 'immortal time'. Int J Epidemiol 2014;43:949-961.
- Lash TL, VanderWeele TJ, Haneuse S, Rothman KJ. Modern Epidemiology, Fourth Edition. Philadephia: Wolters Kluiwer: 2021:73.

4 l'ExtraTerrestre 6 aprile 2023

L'INCHIESTA

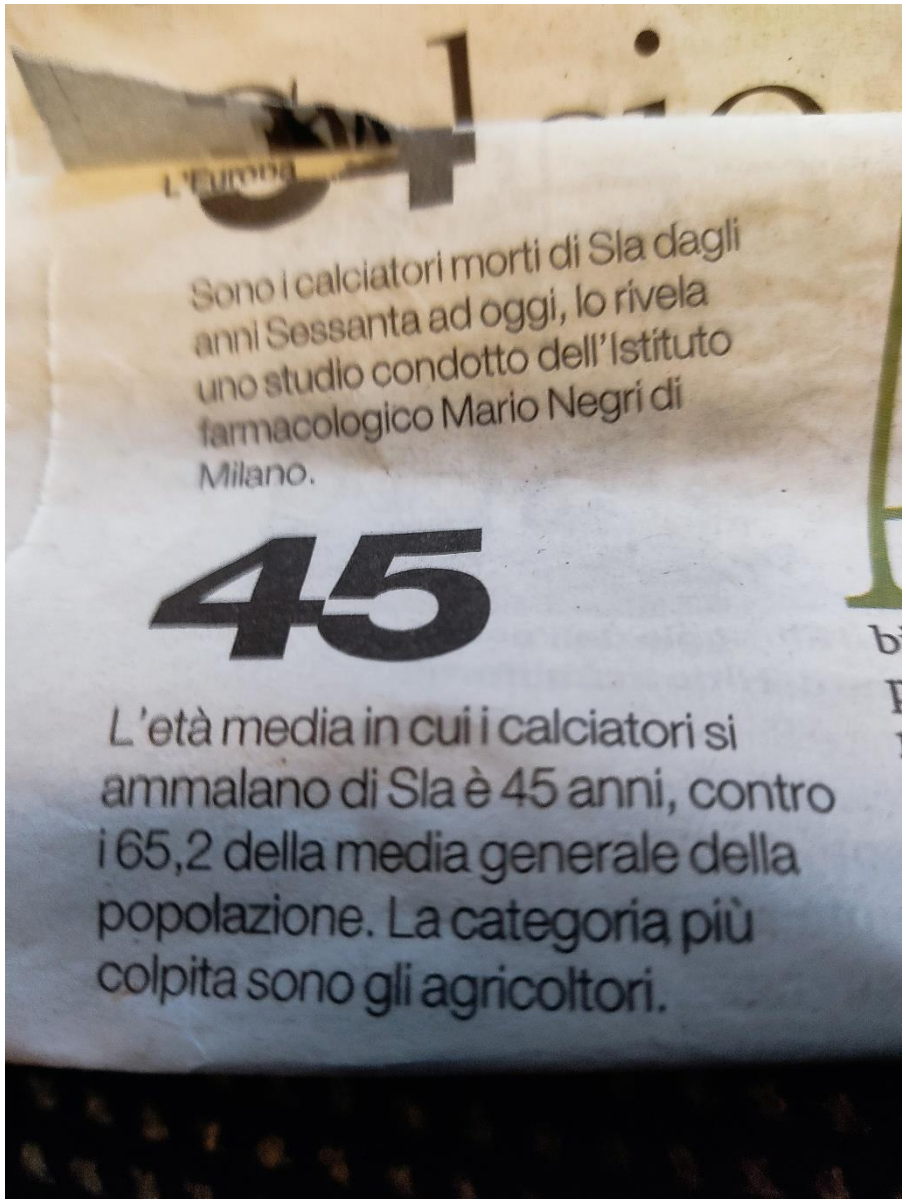
Calcio e Sla, un legame pesticida

34

Sono i calciatori morti di Sla dagli anni Sessanta ad oggi, lo rivela uno studio condotto dell'Istituto farmacologico Mario Negri di

PASQUALE COCCIA

Acque agitate nel mondo del calcio a causa delle acque inquinate, una delle possibili cause della Sla tra i calciatori. Il morbo del pallone fino a oggi ha ucciso 34 giocatori. Il silenzio del mondo del calcio è imbarazzante, nulla e nes-



L'Europa

Sono i calciatori morti di Sla dagli anni Sessanta ad oggi, lo rivela uno studio condotto dell'Istituto farmacologico Mario Negri di Milano.

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L'età media in cui i calciatori si ammalano di Sla è 45 anni, contro i 65,2 della media generale della popolazione. La categoria più colpita sono gli agricoltori.

Pupillo E, Bianchi E, Vanacore N, Montalto C, Ricca G, Robustelli Della Cuna FS, Fumagalli F, Castellani M, Poli F, Romeo F, Tommasi D, Lazzaro P, Beghi E. Increased risk and early onset of ALS in professional players from Italian Soccer Teams. Amyotroph Lateral Scler Frontotemporal Degener. 2020 Aug;21(5-6):403-409. doi: 10.1080/21678421.2020.1752250

Abstract

Objective: Since the observation of several deaths from amyotrophic lateral sclerosis (ALS) among Italian professional soccer players, an association between ALS and soccer has been postulated. The objective of the study is to investigate the association between professional soccer and the risk of ALS in a large cohort of former professional soccer players with prolonged follow-up. *Methods*: All professional soccer players practicing in the period 1959-2000 were identified through the archives of an Italian soccer cards publisher. For each player, date and place of birth, playing role, and team history were recorded. Each player was followed since 15 years of age. Incident ALS cases were all soccer players first diagnosed during the period 1959-2018. The expected incidence rate was the number of ALS cases/100,000 person-years expected in the cohort. SIR was the ratio between observed and expected incidence rate. *Results*: 34 ALS cases were detected. The number of expected cases was 17.8. The SIR was 1.91 (95% CI 1.32-2.67) in the entire sample and 4.66 (95% CI 2.66-7.57) in subjects aged less than 45 years. **The mean age at diagnosis was 45.0 years. Compared to the mean age of onset of ALS in the general population (65.2 years), the disease in former soccer players occurred 20.2 years earlier.** *Conclusions*: Professional soccer players are at higher risk of developing ALS than the general population. Soccer players with ALS develop the disease at a younger than expected age.

Malignant mesothelioma diagnosed at a younger age is associated with heavier asbestos exposure

Tommaso A. Dragani[*,†], Francesca Colombo, Elizabeth N. Pavlisko[1] and Victor L. Roggli[1]

Asbestos exposure is the main etiology of malignant mesothelioma, but there are conflicting data on whether the intensity of exposure modulates the development of this disease. This study considered 594 patients with malignant mesothelioma for whom count data on asbestos bodies and fibers (per gram of wet lung tissue) were available. The relationships between age at diagnosis (a time-to-event outcome variable) and these two measures of internal asbestos exposure, along with other possible modulating factors (sex, tumor location, histological subtype and childhood exposure), were assessed on multivariable Cox proportional hazard models, stratifying by decade of birth year. For both measures of asbestos in lung tissue, younger age at diagnosis was associated with higher internal measures of exposure to asbestos. Stratified Cox analyses showed that for each doubling in asbestos body count patients were 1.07 times more likely to be diagnosed at a younger age [hazard ratio (HR) = 1.07; 95% confidence interval (CI), 1.04–1.09; $P = 2.2 \times 10^{-7}$] and for each doubling in asbestos fiber count patients were 1.13 times more likely to be diagnosed at a younger age (HR = 1.13; 95% CI, 1.09–1.17; $P = 8.6 \times 10^{-11}$). None of the other variables considered were associated with age at diagnosis. Our finding that tumors become clinically apparent at a younger age in heavily exposed subjects suggests that asbestos is involved not only in the malignant mesothelioma tumor initiation but, somehow, also in the progression of the disease.

Carcinogenesis, 2018, Vol. 39, No. 9, 1151–1156

LETTER TO THE EDITOR

Comment on: Malignant mesothelioma diagnosed at a younger age is associated with heavier asbestos exposure

Enrico Oddone[1,2,*], Benedetto Terracini[3], Dario Mirabelli[3], Carolina Mensi[4], Dario Consonni[4] and Francesco Barone-Adesi[5]

LETTER TO THE EDITOR

Letter to the editor re: Dragani *et al.* (2018), 'Malignant mesothelioma diagnosed at a younger age is associated with heavier asbestos exposure'

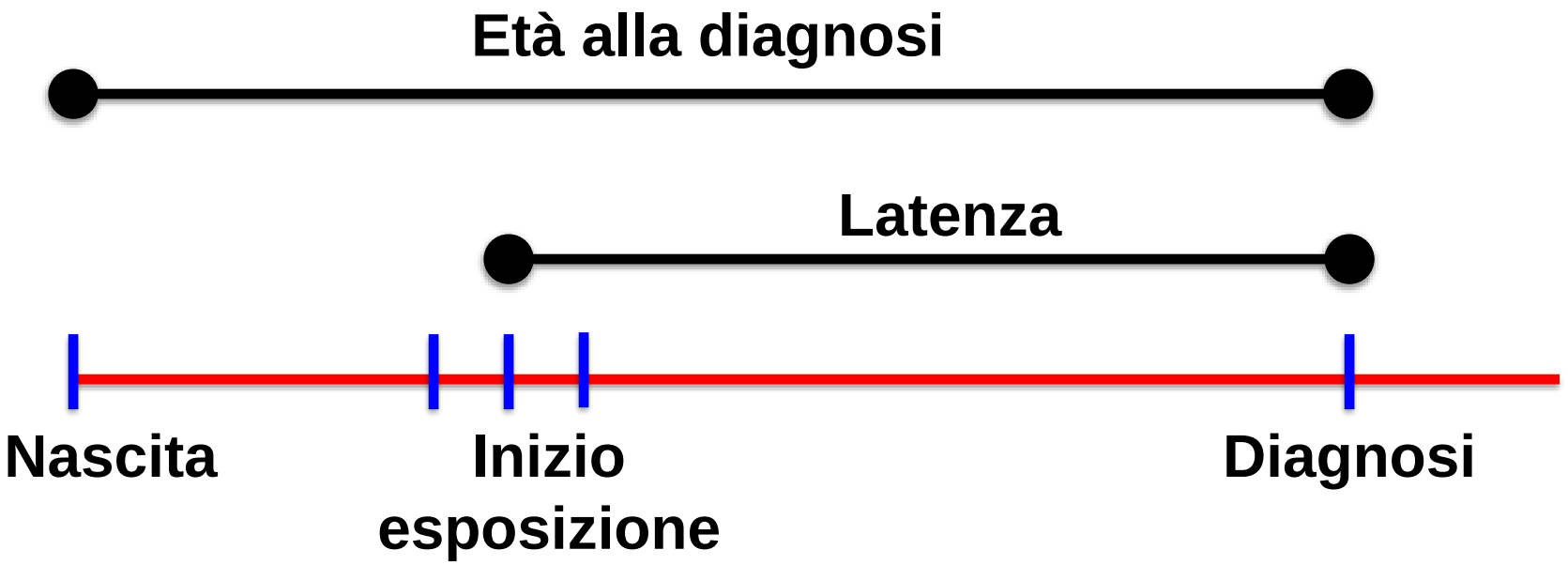
Andrea Farioli[1,*], Stefano Mattioli[1], Stefania Curti[1], Giovanna Spatari[2] and Francesco Saverio Violante[1]

2. Latenza
(tempo dalla prima esposizione)

Similitudine tra età alla diagnosi e latenza

Età alla diagnosi = (**data diagnosi** – data di nascita)
Latenza = (**data diagnosi** – data inizio esposizione)

Una più breve latenza **non** deriva da un “anticipo di malattia”, ma più plausibilmente da un “ritardo di inizio esposizione” (i malati con latenza più breve hanno iniziato ad essere esposti in anni più recenti



The latency period of mesothelioma among a cohort of British asbestos workers (1978–2005)

British Journal of Cancer (2013) 109, 1965–1973

G Frost*,1

Background: The Great Britain (GB) Asbestos Survey is a prospective cohort of asbestos workers in GB. The objective of this study was to investigate determinants of mesothelioma latency, paying particular attention to indicators of intensity of asbestos exposure such as occupation, sex, and presence of asbestosis.

Methods: The analysis included members of the cohort who died with mesothelioma between 1978 and 2005. The primary outcome was the latency period defined as the time from first occupational exposure to asbestos to death with mesothelioma. Generalised gamma accelerated failure-time models were used to estimate time ratios (TRs).

Results: After excluding missing data, there were 614 workers who died with mesothelioma between 1978 and 2005. Total follow-up time was 9280 person-years, with a median latency of 22.8 years (95% confidence interval (CI) 16.0–27.2 years). In the fully adjusted model, latency was around 29% longer for females compared with males (TR = 1.29, 95% CI = 1.18–1.42), and 5% shorter for those who died with asbestosis compared with those who did not (TR = 0.95, 95% CI = 0.91–0.99). There was no evidence of an association between latency and occupation.

Conclusion: This study did not find sufficient evidence that greater intensity asbestos exposures would lead to shorter mesothelioma latencies.

Ma andava fatto su tutti i lavoratori, NON solo sui casi (approccio statistico corretto, approccio epidemiologico errato)

Comment on 'The latency period of mesothelioma among a cohort of British asbestos workers (1978–2005)': methodological problems with case-only survival analysis

D Consonni*[,1], F Barone-Adesi[2] and C Mensi[1]

British Journal of Cancer (2014) 111, 1674 | doi: 10.1038/bjc.2013823

Comment on 'The latency period of mesothelioma among a cohort of British asbestos workers (1978–2005)'

D Mirabelli*[,1] and D Zugna[1]

British Journal of Cancer (2014) 111, 1675 | doi: 10.1038/bjc.2014111

3. Correlazione tra Durata Lavoro o Esposizione e Latenza

Ann. Rev. Public Health. 1988. 9:451–82

MODELS FOR EXPOSURE-TIME-RESPONSE RELATIONSHIPS WITH APPLICATIONS TO CANCER EPIDEMIOLOGY

Duncan C. Thomas

For all these reasons, the description of latency is only meaningful if set in the context of rates with person-years denominators, including appropriate treatment of the time-dependent nature of the exposure variables. A simple

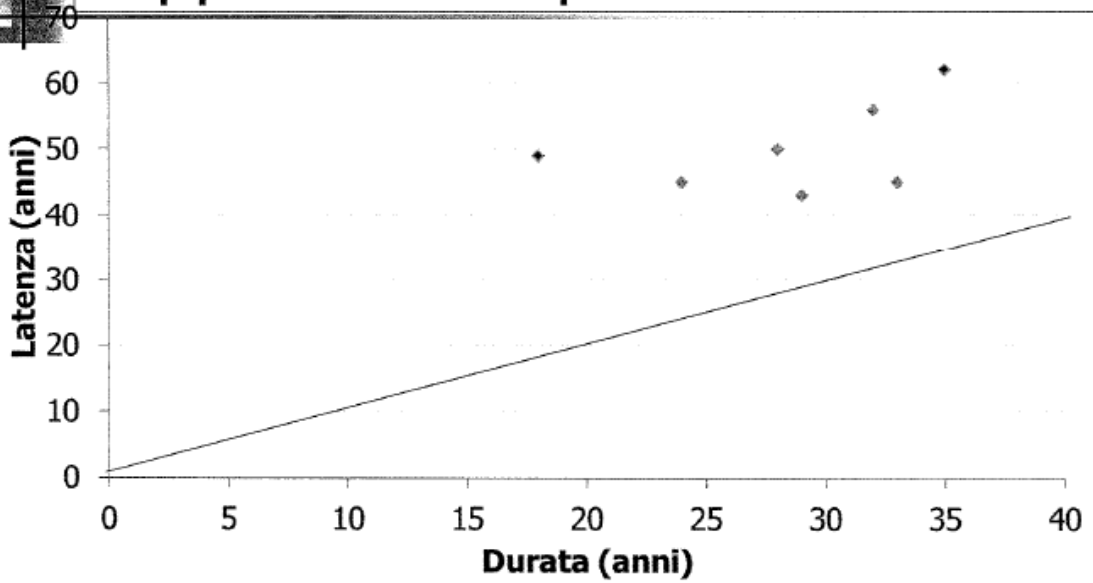
Latency Analysis in Epidemiologic Studies of Occupational Exposures: Application to the Colorado Plateau Uranium Miners Cohort

AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 35:246–256 (1999)

Bryan Langholz, PhD,* Duncan Thomas, PhD, Anny Xiang, PhD, and Daniel Stram, PhD

diseases has long been recognized (Armenian, 1987). Early attempts to characterize the latent period were based on the simple idea of tabulating the time from exposure to disease in those who experienced both in order to get a "latency distribution." This technique was shown to be seriously flawed. In particular, this distribution is completely dependent on the length of follow-up of the study group. The longer the group was followed, the longer the apparent mean latency since new cases would always have longer time to disease than those previously followed (Enterline and Henderson, 1973; Peto, 1985; Thomas, 1987). This phenomenon is precisely the motivation for methods that accommodate censoring in failure time data. Thus, it is natural to apply the methods for censored survival data that serve as the basis for standard statistical methods used in the study of variation in rates used in epidemiologic studies. In this context, latency will be quantified as the evolution of the rate, or more relevantly, the rate ratio relative to unexposed subjects, as a function of time since exposure (Thomas, 1983, 1987; Finkelstein, 1991).

Relazione durata-latenza nei supposti casi a processo



Supposti casi di cui a processo con esposizione ambientale in rosso
Coefficiente di correlazione 0.44, p-value 0.32

E' chiaro quindi che, nei lavoratori in questione, all'aumentare dell'esposizione la latenza non diminuisce ma, semmai, aumenta.

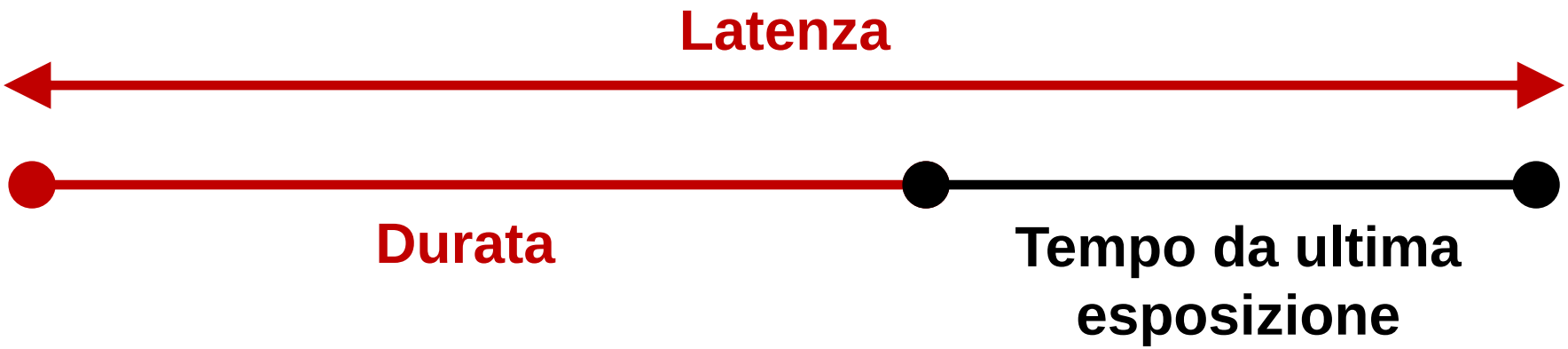
Non vi è relazione inversa tra durata di esposizione e latenza – ossia l'aumentare dell'esposizione non riduce la latenza.

- Processo Montefibre 2017, Torino
- Diapositiva e commenti di uno statistico (>2500 citazioni in PubMed) consulente della difess

- La Durata è inclusa nella Latenza:

Latenza = Durata + Tempo da ultima esposizione

- La Latenza è **direttamente proporzionale** alla Durata (durate lunghe non possono avere latenze brevi), quindi una correlazione positiva è attesa su basi puramente **matematiche**



4. Principi epidemiologici e statistici
Anticipazione di malattia/decesso: come si calcola?

Accelerated Failure Time (AFT) models

- Approccio statistico «classico», in uso da molto tempo
- Modelli di regressione parametrici (modelli esponenziale, lognormale, log-logistico e di **Weibull**)

Nei modelli esponenziale e di Weibull l'effetto di un agente può essere espresso sia come **Hazard Ratio (HR)**, sia come **Time Ratio (TR)**, rapporto tra tempi mediani all'evento)

- In caso di agenti tossici, HR>1 (rischio aumentato) e quindi **TR<1 (anticipazione)**
- In caso di esposizione benefiche, HR<1 (rischio diminuito) e **TR>1 (posticipazione)**

NB: questi modelli sono applicabili anche a sistemi NON biologici (es. prodotti industriali, per valutarne la durata)

RAP

Risk and Rate Advancement Periods as Measures of Exposure Impact on the Occurrence of Chronic Diseases

Hermann Brenner,[1] *Olaf Gefeller,*[2] *and Sander Greenland*[3]

Epidemiology May 1993, Volume 4 Number 3

Education Corner

On the interpretation of risk and rate advancement periods

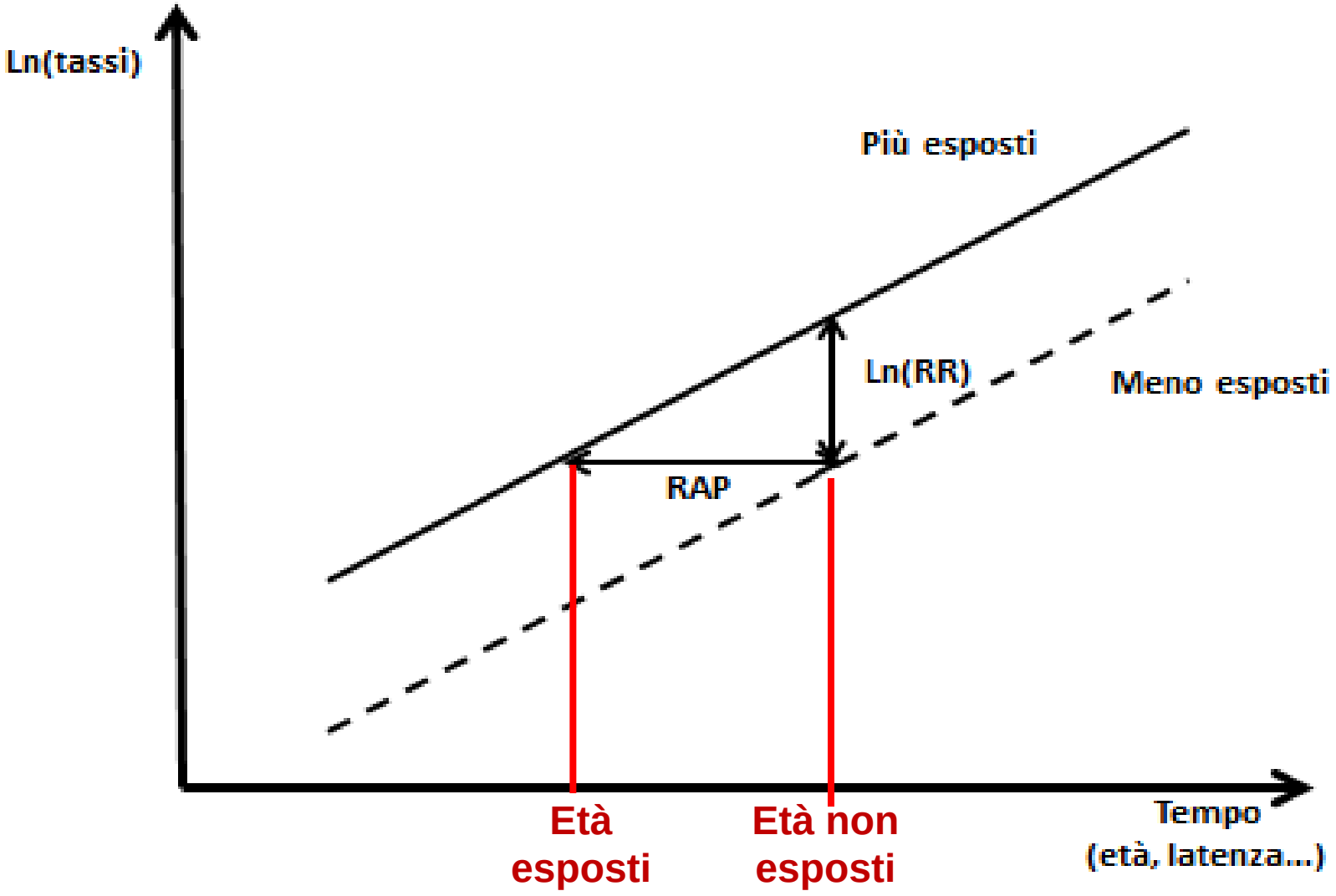
Andrea Discacciati,[1,2]* Andrea Bellavia,[1,2] Nicola Orsini,[1,2] and Sander Greenland[3,4]

International Journal of Epidemiology, 2016, 278–284

RAP – Anticipazione

- **RAP**: differenza fra età a cui i non esposti raggiungono lo stesso tasso degli esposti
- Utilizzabile con modelli di **Poisson, Cox, logistico**
- **Utilizzato in vari articoli** per vari determinanti (fumo, dislipidemia, ipertensione, inquinamento atmosferico, alcool) e varie malattie (cardiovascolari, polmonari, diabete, tumori) (Liese. AJE 2000; Gellert. Tob Control 2013; Finkelstein. AJE 2004; Ferrari. BMJ Open 2014; Mons. BMJ 2015; Ordonez-Mena. BMC Med 2016)

- Ma qualche Professore di Medicina del Lavoro obiettava: non è stato dimostrato per I mesoteliomi; e non c'è un modello biologico


Ln(tassi)
Più esposti
Ln(RR)
Meno esposti
RAP
Età
esposti
Età non
esposti
Tempo
(età, latenza...)

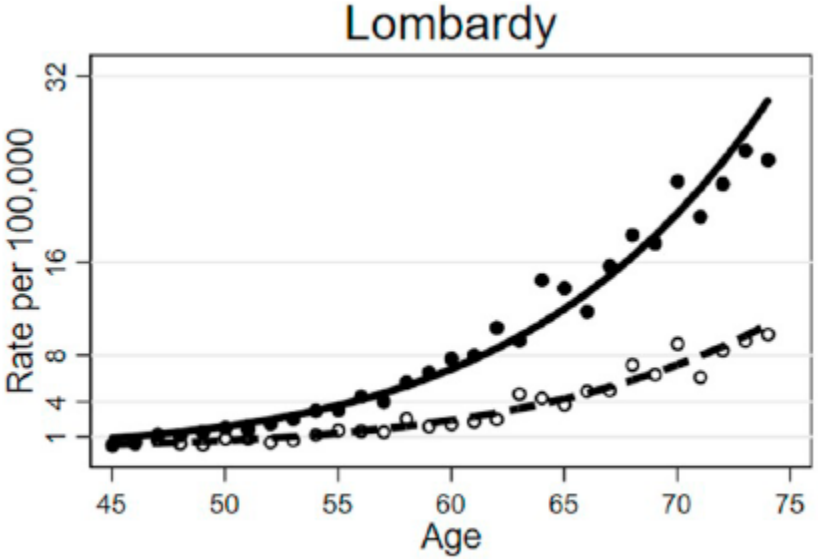
Gender differences in pleural mesothelioma occurrence in Lombardy and Piedmont, Italy

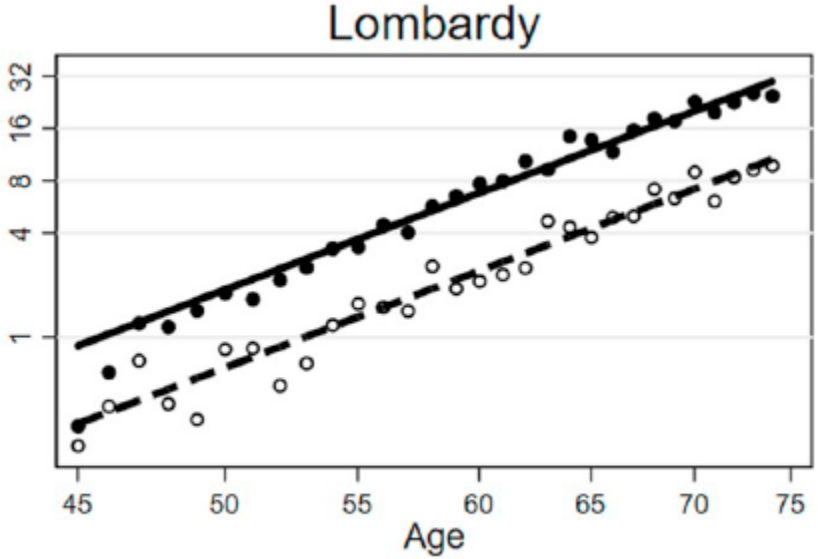
Dario Consonni[a,*], Enrica Migliore[b], Francesco Barone-Adesi[c], Barbara Dallari[a], Sara De Matteis[d], Enrico Oddone[e], Angela C. Pesatori[a,f], Luciano Riboldi[a], Dario Mirabelli[b], Carolina Mensi[a]

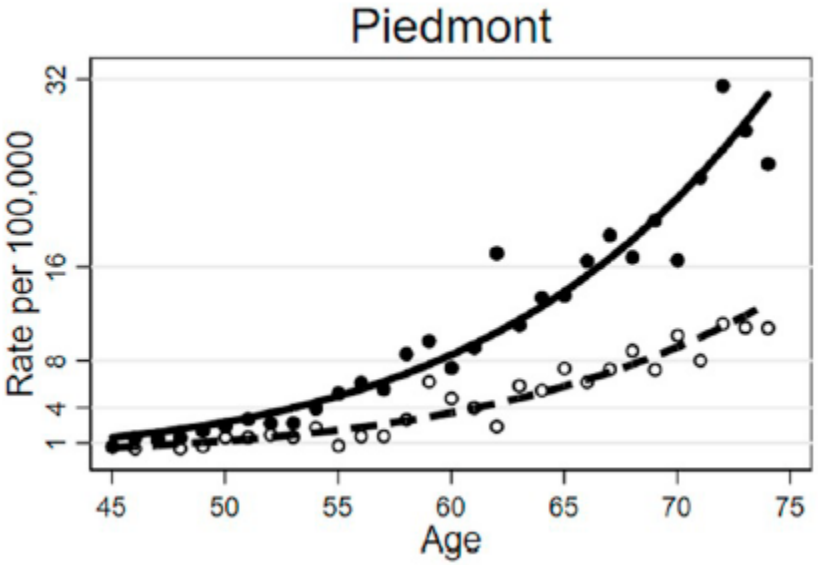
Background: Higher mesothelioma rates in men (vs women) reflect more frequent and more intense asbestos exposure. We assessed the impact of exposure difference between genders on age-specific rates of pleural mesothelioma (PM) occurrence using data from two Italian regions.
Methods: We used data from the Lombardy and Piedmont mesothelioma registries (period 2000–2016, age 45–74 years) to compare rates of PM in men and women and to estimate the rate advancement period (RAP).
Results: Based on 3384 cases (2405 men, 979 women) in Lombardy and 2042 (1389 men, 653 women) in Piedmont, the rate ratio was 2.81 (90% confidence interval: 2.61–3.03) in Lombardy and 2.39 (2.17–2.62) in Piedmont. In both regions RAP ranged from 7 to 10 years (at age 45 and 63 in men, respectively).
Conclusion: Men showed more than twofold increased PM rates and reached the same incidence as women 7–10 years earlier. RAP can be a useful measure of exposure impact on premature disease occurrence.

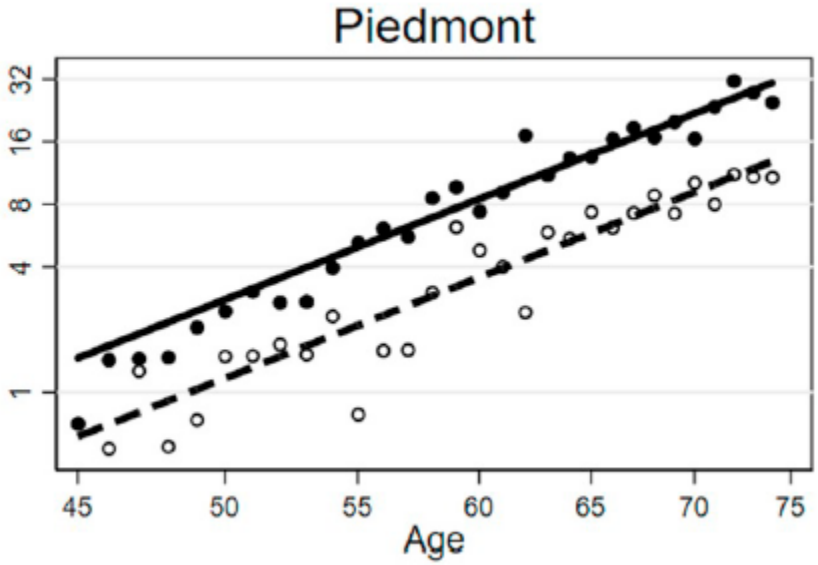
Environmental Research 177 (2019) 108636

Tassi per età (45-74 anni)









P-value per interazione Genere-Età: 0.76 (L) e 0.33 (P):

- **Tassi di MP** aumentati **2-3 volte** negli **uomini** (indubbia maggiore esposizione lavorativa) nelle 2 regioni
- Tali eccessi di rischio si traducono in una **insorgenza anticipata** negli uomini di **7-10 anni**
- Se avessimo (erroneamente) usato **età alla diagnosi**: netta sottostima (3 anni in Lombardia, 1.6 anni in Piemonte)

Rate advancement measurement for lung cancer and pleural mesothelioma in asbestos-exposed workers

Danila Azzolina,[1] Dario Consonni,[2] Daniela Ferrante,[3] Dario Mirabelli,[4] Stefano Silvestri,[3] Ferdinando Luberto,[5] Alessia Angelini,[3] Francesco Cuccaro,[6] Anna Maria Nannavecchia,[6] Enrico Oddone,[7] Massimo Vicentini,[5] Francesco Barone-Adesi,[8] Tiziana Cena,[3] Lucia Mangone,[5] Francesca Roncaglia,[5] Orietta Sala,[9] Simona Menegozzo,[10] Roberta Pirastu,[11] Sara Tunesi,[3] Elisabetta Chellini,[12] Lucia Miligi,[12] Patrizia Perticaroli,[13] Aldo Pettinari,[13] Vittoria Bressan,[14] Enzo Merler,[15] Paolo Girardi,[15,16] Lucia Bisceglia,[17] Alessandro Marinaccio,[18] Stefania Massari,[18] Corrado Magnani ,[3] The working group

Azzolina D, *et al*. *Thorax* 2022;**0**:1–8. doi:10.1136/thoraxjnl-2021-217862

Rate advancement measures

The classical approach to calculating disease rate advancement is based on AFT models that can be computed via exponential, log-normal, log-logistic or Weibull parametrizations. In the exponential and Weibull models, the effect of an agent can be expressed both as an HR (ie, the ratio between hazards of event occurrence) or as a TR[34] (the ratio between times to the event). In the case of a noxious agent, HR > 1 indicates an increased risk and therefore corresponds to a TR < 1 (acceleration or advancement). On the contrary, in the case of a beneficial effect, we observe HR < 1 and TR > 1 (deceleration or postponement). The

Conclusioni

- Non usare età/latenza alla diagnosi nei soli casi
- Non calcolare correlazione tra durata e latenza nei soli casi
- **Seguire principi epidemiologici e statistici e utilizzare metodi appropriati basati su tassi, rischi, odds (AFT, RAP)**