Shift work and chronic disease: the epidemiological evidence

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Con il termine "Shift work" si intendono tutti quei turni di lavoro svolti in orari "sregolati" o inusuali, compreso il lavoro notturno e il lavoro a turni "a rotazione".

Un recente rapporto (2007) sulle condizioni di lavoro in Europa mostra come circa il 20% dei lavoratori è è coinvolto in qualche modo nel lavoro a turni.

Obiettivo

Non è ancora stato pubblicato un riassunto generale delle prove dell'associazione tra il lavoro a turni e le malattie croniche.

L'obiettivo di questa revisione è di aggiornare i ricercatori e medici del lavoro sulle conoscenze attuali su questo tema, con lo scopo di stimolare una discussione ad ampio raggio sul tema del lavoro a turni e delle malattie croniche.

Questa revisione descrive i risultati descritti nelle reviews sistematiche e analizza/critica i risultati ottenuti negli studi più recenti.

Metodi

- **Ricerca su PubMed al 31 dicembre 2009.**

  Parole chiave:
  - **'work schedule tolerance' or 'shift work'**
  - **key words for each of the chronic diseases or conditions of interest (e.g. 'cancer')**
  - **other key words ('survival rate' or 'mortality' or 'morbidity' or 'odds ratio' or 'incidence' or 'risk')**

550 risultati ottenuti

- **Sono esclusi:**
  - articoli non scritti in inglese
  - clinical trials o practice guidelines o randomized controlled trials
  - non ha l'abstract disponibile

- Sono stati inclusi gli studi che presentano, oltre ad analisi sul gruppo composto da lavoratori a turni, anche il confronto con un gruppo di riferimento costituito da lavoratori giornalieri o da lavoratori che hanno prevalentemente lavorato in turni diurni.

- Sono state recuperate manualmente alcune pubblicazioni/revisioni che corrispondono ai criteri di selezione.

Valutazione delle evidenze

Box 1. The modified RCGP three-star system

- '***' Strong evidence — provided by generally consistent findings in multiple, high-quality scientific studies;
- '**' Moderate evidence — provided by generally consistent findings in fewer, smaller, or lower quality scientific studies;
- '*' Limited or contradictory evidence — provided by one scientific study or inconsistent findings in multiple scientific studies and
- '–' No scientific evidence — based on clinical studies, theoretical considerations and/or clinical consensus.

Risultati – OUTCOME: cancro (in particolare cancro al seno)

Authors	Study	Findings
Cancer		
Lahti *et al.* [26]	Cohort study of general population in Finland with non-Hodgkin's lymphoma as outcome and 10 year-lagged cumulative night shift work as exposure. F: cases: 1337 unexposed, 1157 exposed; M: cases: 2286 unexposed, 1527 exposed (25–64 at census).	RR = 1.10 (95% CI 1.03–1.19) in men; RR = 1.02 in women (95% CI 0.94–1.12). Covariates were age, social class, cohort period.
Review		
Straif *et al.* [10] 2007	Summary of findings by the International Agency for Research on Cancer (IARC) working group on the carcinogenicity of shift work.	On the basis of 'limited evidence in humans for the carcinogenicity of shift work that involves night work' and 'sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)', the working group concluded that 'shift work that involves circadian disruption is probably carcinogenic to humans'.
Megdal *et al.* [19] 2005	Night work and breast cancer: a systematic review of 13 studies, 7 of which are on airline cabin crew.	Night work was associated with an increased risk of breast cancer.
Kolstad [20] 2008	A systematic review on the relationship between night shift work and breast cancer and other cancers: of 13 studies included, 8 studies looked at breast cancer, 3 at prostate cancer, 3 at colon cancer and 4 at all cancers combined.	Based on data published to May 2007, concluded that there was suggestive but not conclusive evidence that long-term night shift work (≥20 years) increased the risk of breast cancer. There was a lack of evidence on the association of night shift work and risk for cancer at other sites.
Hansen [22]	Discussion of previous evidence and ongoing studies in Denmark focussing on the relationship between melatonin, night shift work and breast cancer.	Previous evidence was relatively consistent for an increased risk of breast cancer in women working at non-day time.
Davis and Mirick [21]	Discussion of previous evidence and ongoing studies in Seattle (United States), focussing on the relationship between light at night, night shift work and breast cancer.	Evidence from the studies carried out in Seattle supported the hypothesis that the exposure to night work is associated with an increased risk of breast cancer.

F, female; M, male.

Metanalisi: RR 1.48 (I.C.: 1.36-1.91)

OUTCOME: cancro alla prostata

- Kubo et al. (2006) – studio prospettico - RR: 3
- Conlon et al. (2007) – studio caso-controllo – associazione significativa
- Schwartzbaum et al. (2007) – non trovata un'associazione significativa.

OUTCOME: cancro del colon-retto

- Evidenze limitate e inconsistenti

OUTCOME: cancro in altre sedi

- Lahti et al. (2008) hanno indagato 3813 uomini e 2494 donne che hanno sviluppato il linfoma non-Hodgkin durante un follow-up in una coorte finlandese di 1.669.272 individui.
- È stata trovata un'associazione significativa tra il lavoro notturno e il rischio di linfoma non-Hodgkin negli uomini (RR = 1.10, 95% I.C.: 1,03-1,19), ma non nelle donne (RR = 1.02, I.C.: 95% 0,94-1,12).

OUTCOME: cancro in tutte le sedi combinate

- Quattro studi hanno esaminato la relazione tra il lavoro a turni e il rischio di cancro complessivo (mortalità o di incidenza), ma nessuno offre una forte evidenza di un'associazione positiva.
- Schwartzbaum et al. (2007) non hanno trovato un’associazione significativa tra il lavoro a turni. L'incidenza è 1,00 (95% CI 0,89-1,13) nelle donne e 1,02 (95% CI 1,00-1,05) negli uomini, per i turnisti rispetto ai non turnisti.

IN CONCLUSIONE:

- vi è evidenza “suggestiva” di un'associazione a lungo termine fra lavoro notturno (da più di 20 anni) e un aumento del rischio di sviluppare il cancro al seno. L'evidenza epidemiologica risulta quindi essere moderata (RCGP **).
- Le prove per le associazioni tra il lavoro a turni e tumori in altri siti e tutti i tumori combinati sono limitati (RCGP *)

OUTCOME: problemi cardiovascolari

Non è chiaro il disegno di studio e l'aggiustamento del modello

Authors	Study design	Population (age)	Population and occupation (Location)	Outcomes	Main exposure/ referents	Main results	Covariates
CVD							
Ellingsen *et al.* [33]	'Case series of cohort'[a]	M: 223 cases: CAD or MI—27 shift workers, 40 day workers; other atherogenic vascular diseases—61 shift workers, 95 day workers	Workers in a fertiliser plant (Qatar)	CAD or MI; other atherogenic vascular diseases	Rotating shift work (8 h rotating shift: 2 mornings, 2 afternoons, 2 nights and 2 days of rest)/day work	RR = 1.65 (95% CI 1.38–1.97) of cardiovascular events.	Model adjustments not specified, but implied using S, BMI, diabetes, senior or intermediate staff
Hermansson *et al.* [35]	Nested case-control	F: 65 day worker cases, 23 shift worker cases; 136 day worker controls, 49 shift worker controls; M: 85 day worker cases, 21 shift worker cases, 183 day worker controls, 45 shift worker controls (mean age: 54.7)	Combination of two population-based health surveys (Sweden)	Ischaemic stroke	Shift work/day work	RR = 1.0 (95% CI 0.6–1.8) of ischaemic stroke	Age-adjusted. Other models with similar results: (1) age, job strain, S, low educational level; (2) high serum triglycerides, high serum total cholesterol, high BP
Haupt *et al.* [34]	Cross-sectional	F: 1052 unexposed, 192 exposed; M: 760 unexposed, 506 exposed (mean age: 61.5 unexposed, 62.3 exposed)	Adult population in West Pomerania (Germany)	Atherosclerosis and MI	Exposed to shift work/unexposed	HR = 1.53 (95% CI 1.06–2.22) of MI at an early age	Age, sex, pack-years smoking
Brown *et al.* [36]	Cohort	F: 28 015 never, 36 400 1–14 years, 3821 15–29 years, 1187 ≥30 years [mean age: 54.5 (never), 55.0 (1–14 years), 56.3 (15–29 years), 60.4 (≥30 years)]	Nurses (USA)	Ischaemic stroke	Rotating night shift work (at least three nights per month in addition to days and evenings in that month) for 1–2, 3–5, 6–9, 10–14, 15–19, 20–29 and ≥30 years/never	HR = 1.04 (95% CI 1.01–1.07) of ischemic stroke per 5 years working rotating night shifts	Age, questionnaire cycle, hypertension, CHD, diabetes, elevated cholesterol, aspirin use, S, AL, PA, BMI, fruit and vegetable intake, menopausal status and use of hormone replacement therapy

OUTCOME: problemi cardiovascolari

Review		
Frost *et al.* [7] 2009	Shift work and ischaemic heart disease: a systematic review	14 Studies were reviewed, of which 7 studied fatal events, 6 combined fatal and non-fatal events and 1 study separated fatal and non-fatal events. Conclusion: 'There is limited epidemiologic evidence for a causal relation between shift work and ischemic heart disease'.[7]
Boggild and Knutsson [32] 1999	Shift work and CVD: a systematic review	17 Studies were reviewed. Conclusion: '[…] the most reasonable risk estimate seems still to be the relative risk of 1.4 derived from the hitherto methodologically most convincing study by Knutsson *et al.* [30] whose results are supported by the demonstration of a dose-response and an equal risk for both genders'.
Kristensen [31] 1989	Work environment and CVD: a critical review	Included a section of shift work. Conclusion: 'The relative risk of 1.4 found by Knutsson *et al.* [30] is consistent with the results of other studies in the field and must, for the present, be regarded as the most reasonable estimate'.
Åkerstedt *et al.* [29] 1984	Shift work and CVD: a critical review	The first review on the relationship between shift work and CVD. Conclusion: The up-to-date evidence on the association between shift work and CVD is suggestive of an adverse association.

OUTCOME: problemi cardiovascolari

IN CONCLUSIONE:

- Le revisioni sistematiche e quelle critiche forniscono evidenze “suggestive”, ma non conclusive dell’associazione tra CVD e shift work.
- Le ultime ricerche forniscono nuove prove di un’associazione inversa.
- L'evidenza epidemiologica dell'associazione tra lavoro a turni e malattie cardiovascolari risulta quindi essere moderato (RCGP **)

OUTCOME: Sindrome metabolica

- Con il termine “sindrome metabolica” si intende un insieme di fattori di rischio (che spesso avvengono simultaneamente), che sono:
  - Obesità
  - Pressione sanguinea elevata
  - Trigliceridi elevati
  - Colesterolo alto
  - Elevata glicemia a digiuno
- I criteri che definiscono la sindrome metabolica sono stati sviluppati nell’ultimo decennio
- Vi sono 4 definizioni della sindrome metabolica. Questo incide sui risultati ottenuti nelle analisi.

OUTCOME: Sindrome metabolica

Authors	Study design	Population (age)	Population and occupation (Location)	Outcomes	Main exposure/ referents	Main results	Covariates
Metabolic syndrome							
Karlsson *et al.* [44]	Cross-sectional	F: 4632 shift workers, 9857 day workers; M: 3277 shift workers, 9719 day workers (aged 30, 40, 50, or 60)	General population (Sweden)	Metabolic syndrome (no uniform definition was used; components were defined separately)	Shift work/day work	F: RR = 1.71 ($P < 0.0001$); M: RR = 1.63 ($P < 0.0001$) of having all three components (obesity, hypertension, and high triglycerides)	Age
Sookoian *et al.* [45]	Cross-sectional	M: 474 rotating shift workers, 877 day workers (mean age: 36 rotating shift workers, 34 day workers)	Healthy workers from a factory (Argentina)	Metabolic syndrome (NCEP-ATPIII definition)	Rotating shift work/ day work	OR = 1.51 (95% CI 1.01–2.25)	Age, PA
Esquirol *et al.* [46]	Cross-sectional	M: 100 shift workers; 98 day workers (mean age: 46.54 shift workers; 48.84 day workers)	Workers employed in a chemical plant (France)	Metabolic syndrome (NCEP-ATPIII and IDF definitions)	Rotating shift work (8 h rotating shift: 1 or 2 mornings, 1 or 2 afternoons, 1 or 2 night and 3 or 4 rest days)/day work	OR = 2.38 (95% CI 1.13–4.98) (NCEP-ATPIII); OR = 0.95 (95% CI 0.51–1.78) (IDF)	Age, work organization, total PA, Job Strain Index, S, AL, glucose intake, total energy intake and eating intermediate meals except lunch and dinner
De Bacquer *et al.* [47]	Cohort	M: 1220 day workers, 309 rotating shift workers (35–59 baseline)	Nine different companies and public administrations (Belgium)	Metabolic syndrome (IDF definition)	Rotating shift work/ day work	OR = 1.46 (95% CI 1.04–2.07)	Age, S, PA outside work, education level, job strain, physical job demands; WC, diastolic BP, HDL cholesterol
Pietroiusti *et al.* [48]	Cohort	F: 244 day workers, 278 night workers; M: 92 day workers, 124 night workers (mean age: 38.9 shift workers; 37.9 daytime workers)	Health care workers (Italy)	Metabolic syndrome (updated NCEP definition)	Night shift work or rotating shift work (at least four nights per month during a year)/ daytime work	RR = 5.10 (95% CI 2.15–12.11)	Age, gender, S, AL, WC, family history, sedentariness

OUTCOME: Diabete

Authors	Study design	Population (age)	Population and occupation (Location)	Outcomes	Main exposure/ referents	Main results	Covariates
Diabetes							
Mikuni *et al.* [52] 1983	Cross-sectional	M: 1514 shift workers, 653 day workers	Factory labourers (Japan)	Diabetes	Three-shift/day	Prevalence rate of diabetes: 2.1% in three-shift workers; 0.9% in day workers ($P < 0.05$)	N/A
Kawakami *et al.* [53] 1999	Cohort	M: 1015 shift workers, 1179 day workers	Workers at a large electrical company (Japan)	Diabetes	Rotating shift/day	HR = 1.67 (95% CI 0.57–4.90)	Age, education, BMI, S, AL, leisure time PA, and family history
Nagaya *et al.* [54] 2002	Cross-sectional	M: 826 shift workers, 2824 day workers (46.7 ± 7.0 years)	Blue-collar workers attending annual health check-ups (Japan)	Fasting serum glucose ≥7.00mmol/l or patient under treatment for diabetes	Shift work/day work	Age group 30–39 years OR = 6.75 (95% CI 1.31–56.1); age group 40–49 years OR = 1.22 (95% CI 0.68–2.10); age group 50–59 years OR = 0.93 (95% CI 0.53–1.55)	BMI, job, S, AL and exercise
Karlsson *et al.* [55] 2005	Cohort	M: 2354 shift workers, 3088 day workers	Workers from two pulp and paper manufacturing plants (Sweden)	Mortality due to diabetes	Shift work (<5 years, 5–9 years, 10–19 years, 20–29 years, ≥30 years)/never worked shifts	Trend per year shift work in mortality due to diabetes as an underlying or contributory cause (b(linear coefficient) × 10^{-5} = 4.14, 95% CI 2.46–5.81)	Age
Morikawa *et al.* [56] 2005	Cohort	M: 492 three-shift workers, 228 two-shift workers, 1099 fixed-daytime workers (blue collar); 1041 fixed-daytime workers (white collar)	Blue collar workers in a sash and zipper factory (Japan)	Diabetes	Shift work (two-shift, three-shift) fixed day work	RR = 1.73 (95% CI 0.85–3.52) (two-shift versus day workers); RR = 1.33 (95% CI 0.74–2.36) (three-shift versus day workers)	Age, BMI, family history, S, AL, PA

OUTCOME: Sindrome metabolica e diabete

IN CONCLUSIONE:

- l'interpretazione dei risultati pubblicati è difficile a causa di una serie di questioni tra cui:
  - ambiguità nelle informazioni riportate sul disegno dello studio
  - difficile comparabilità tra modalità di lavoro
  - enfasi sull'aumento dei rischi (non significativi)
  - evidenziare risultati di analisi di sottogruppo
  - insufficienti o poco chiari aggiustamenti del modello
  - assenza di una definizione di sindrome metabolica diffusa ed accettata

OUTCOME: Sindrome metabolica e diabete

IN CONCLUSIONE:

- Per la sindrome metabolica, sulla base dei risultati in gran parte statisticamente significativi, ma con limiti metodologici, l'evidenza epidemiologica risulta essere di grado moderato (RCGP **)
- Per il diabete, basandosi sul fatto che ci sono stati diversi studi, ma solo uno ha segnalato un rischio significativamente elevato tra i lavoratori a turni e le problematiche di cui sopra, l'evidenza epidemiologica è limitata (RCGP *)

MECCANISMI PUTATIVI

CANCRO

- La maggiore esposizione alla luce durante la notte è stato ipotizzato essere in parte responsabile della crescita dell'incidenza del cancro al seno. È stato dimostrato che la luce durante la notte sopprime la secrezione di melatonina.

CANCRO

- Il lavoro a turni è stato anche collegato ad una serie di fattori comportamentali e stile di vita che possono essere associati con il cancro o modificare i rischi associati con il lavoro a turni.
- Per esempio, l'evidenza suggerisce che lavoratori a turni siano più probabilità di essere fumatori e di avere un più alto indice di massa corporea.
- Altri studi hanno dimostrato che i turnisti possono dormire meno e hanno la qualità del sonno inferiore a quello dei lavoratori al giorno.

CVD e condizioni croniche connesse

- Sono state fatte una serie di ipotesi che collegano il lavoro a turni e i disturbi cronici, tra cui:
  - l'interruzione circadiana
  - lo stress, che causa disturbi alle normali funzioni metaboliche e ormonali
  - Comportamenti dannosi, come il fumo e una dieta povera

CONCLUSIONI

Box 2. Future research

Future research priorities may include:

- Large prospective cohort studies of shift workers and non-shift workers with multiple, well-characterized disease end points;
- Further data from a wider variety of occupational groups;
- More detailed information on the spectrum of different aspects of shift work, such as duration, frequency, type and pattern;
- Clearer study methodologies for determining whether certain variables, e.g. smoking and BMI, should be treated as confounders or as explanatory factors in the causal pathway in shift work research; and
- More data on proposed mechanisms, such as on the relationships between: melatonin and cancer; sleep and cancer; melatonin and circadian disruption; and clock gene-variants and chronic disease.